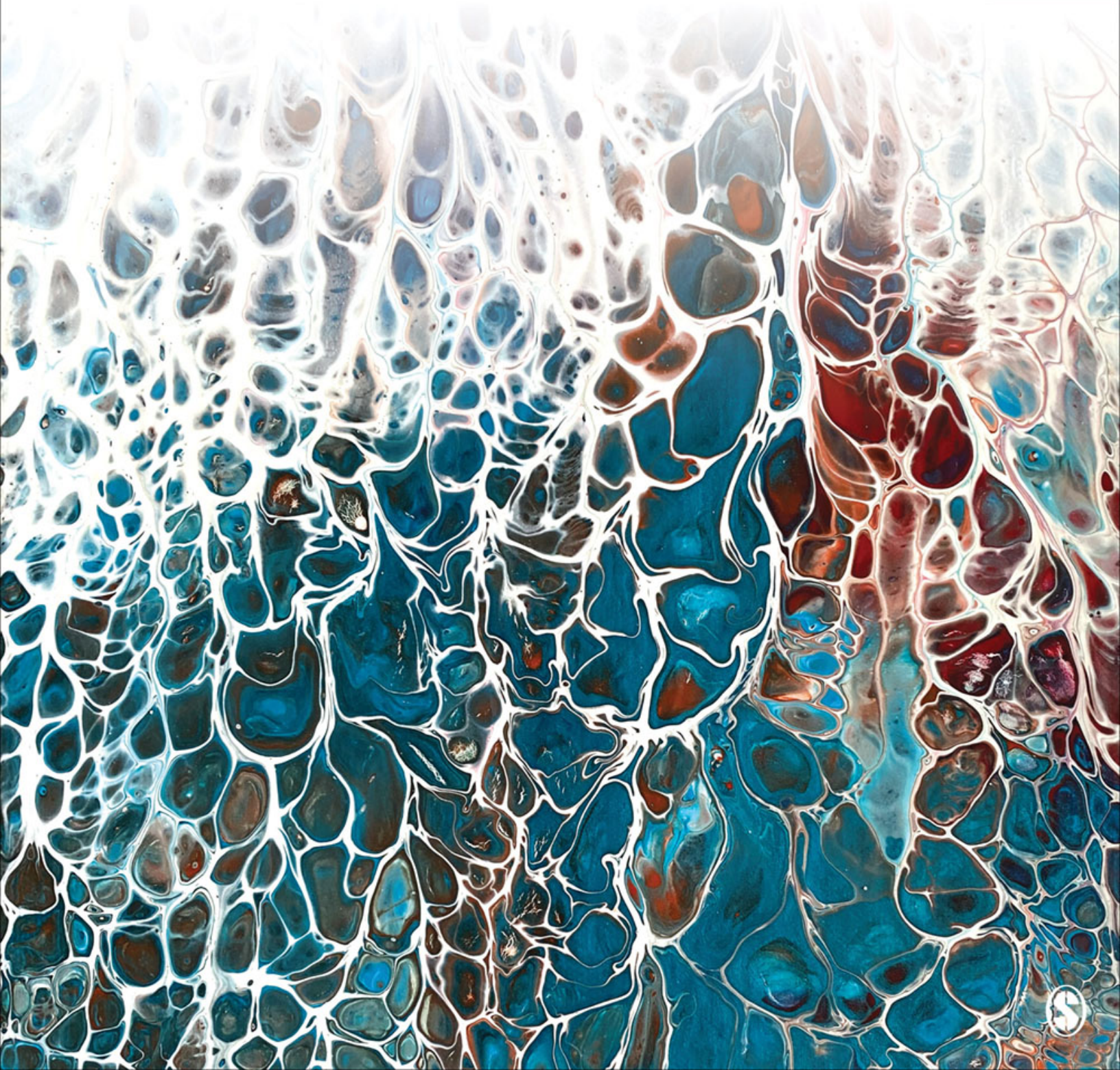
Brain & Behavior

An Introduction to Behavioral Neuroscience

6e

BOB GARRETT / GERALD HOUGH



BRAIN & BEHAVIOR

Sixth Edition

To my late wife, Duejean,

sons Geoffrey and Michael, and

grandchildren Evan, Naomi, and Talia.

—Bob Garrett

To my wife, Kerry,

thank you for being my partner in crime over the last three decades, and for giving me the time to complete this edition.

—Gerald Hough

Sara Miller McCune founded SAGE Publishing in 1965 to support the dissemination of usable knowledge and educate a global community. SAGE publishes more than 1000 journals and over 600 new books each year, spanning a wide range of subject areas. Our growing selection of library products includes archives, data, case studies and video. SAGE remains majority owned by our founder and after her lifetime will become owned by a charitable trust that secures the company's continued independence.

Los Angeles | London | New Delhi | Singapore | Washington DC | Melbourne

BRAIN & BEHAVIOR

An Introduction to Behavioral Neuroscience

Sixth Edition

Bob Garrett

California Polytechnic State University, San Luis Obispo

Gerald Hough

Rowan University

SAGE

Los Angeles | London | New Delhi
Singapore | Washington DC | Melbourne

Los Angeles

London

New Delhi

Singapore

Washington DC

Melbourne

FOR INFORMATION:

SAGE Publications, Inc.

2455 Teller Road

Thousand Oaks, California 91320

E-mail: order@sagepub.com

SAGE Publications Ltd.

1 Oliver’s Yard

55 City Road

London EC1Y 1SP

United Kingdom

SAGE Publications India Pvt. Ltd.

B 1/I 1 Mohan Cooperative Industrial Area

Mathura Road, New Delhi 110 044

India

SAGE Publications Asia-Pacific Pte. Ltd.

18 Cross Street #10-10/11/12

China Square Central

Singapore 048423

Acquisitions Editor: Lara Parra

Content Development Editor: Sam Rosenberg

Editorial Assistant: Elizabeth Cruz

Production Editor: Veronica Stapleton Hooper

Copy Editor: Laureen Gleason

Typesetter: C&M Digitals (P) Ltd.

Proofreader: Rae-Ann Goodwin

Indexer: Integra

Cover Designer: Candice Harman

Marketing Manager: Victoria Velasquez

Copyright © 2022 by SAGE Publications, Inc.

All rights reserved. Except as permitted by U.S. copyright law, no part of this work may be reproduced or distributed in any form or by any means, or stored in a database or retrieval system, without permission in writing from the publisher.

All third party trademarks referenced or depicted herein are included solely for the purpose of illustration and are the property of their respective owners. Reference to these trademarks in no way indicates any relationship with, or endorsement by, the trademark owner.

Printed in Canada

ISBN: 978-1-5443-7348-5

Library of Congress Control Number: 2020915184

This book is printed on acid-free paper.

20 21 22 23 24 10 9 8 7 6 5 4 3 2 1

BRIEF CONTENTS

Preface
About the Authors
Chapter 1 • What Is Behavioral Neuroscience?
Part I. Neural Foundations of Behavior: The Basic Equipment

- Chapter 2 • Communication Within the Nervous System
- Chapter 3 • The Organization and Functions of the Nervous System
- Chapter 4 • The Methods and Ethics of Research

Part II. Motivation and Emotion: What Makes Us Go

- Chapter 5 • Drugs, Addiction, and Reward
- Chapter 6 • Motivation and the Regulation of Internal States
- Chapter 7 • The Biology of Sex and Gender
- Chapter 8 • Emotion and Health

Part III. Interacting With the World

- Chapter 9 • Hearing and Language
- Chapter 10 • Vision and Visual Perception
- Chapter 11 • The Body Senses and Movement

Part IV. Complex Behavior

- Chapter 12 • Learning and Memory
- Chapter 13 • Intelligence and Cognitive Functioning
- Chapter 14 • Psychological Disorders
- Chapter 15 • Sleep and Consciousness

Glossary
References
Author Index
Subject Index

DETAILED CONTENTS

Preface
About the Authors
Chapter 1 • What Is Behavioral Neuroscience?

The Origins of Behavioral Neuroscience

Prescientific Psychology and the Mind-Brain Problem
Descartes and the Physical Model of Behavior
Helmholtz and the Electrical Brain
The Localization Issue

Nature and Nurture

The Genetic Code
The Human Genome Project
Heredity: Destiny or Predisposition?

A Further Look | CRISPR: A New Tool to Edit Genes

Part I. Neural Foundations of Behavior: The Basic Equipment

Chapter 2 • Communication Within the Nervous System

The Cells That Make Us Who We Are

Neurons

A Further Look | Targeting Ion Channels

Glial Cells

How Neurons Communicate With Each Other

Chemical Transmission at the Synapse

A Further Look | A Neuron Type Found Only in Humans

Regulating Synaptic Activity
Neurotransmitters

A Further Look | Agonists and Antagonists in the Real World

Neural Codes and Neural Networks

A Further Look | Uses and Abuses of Artificial Neural Networks
Chapter 3 • The Organization and Functions of the Nervous System
The Central Nervous System
The Forebrain
A Further Look | The Case of Phineas Gage
The Midbrain and Hindbrain
The Spinal Cord
Protecting the Central Nervous System
The Peripheral Nervous System
The Cranial Nerves
The Autonomic Nervous System
Development and Change in the Nervous System
The Stages of Development
A Further Look | Microtubules Move Neurons Along Their Way
How Experience Modifies the Nervous System
Damage and Recovery in the Central Nervous System
A Further Look | Building a Better Brain
A Further Look | Ultrasound Surgery
A Further Look | Mending the Brain With Computer Chips
Chapter 4 • The Methods and Ethics of Research
Science, Research, and Theory
Theory and Tentativeness in Science
Experimental Versus Correlational Studies
Research Techniques
Staining and Imaging Neurons
Light and Electron Microscopy
A Further Look | Looking Into the Brain
Measuring and Manipulating Brain Activity

Brain Imaging Techniques
A Further Look | Scanning King Tut
A Further Look | Growing a Model Brain From Stem Cells

Investigating Heredity
A Further Look | The Brainbow Connection
Research Ethics

Plagiarism and Fabrication
Protecting the Welfare of Research Participants
Gene Therapy
A Further Look | Can Gene Editing Be Regulated?

Stem Cell Therapy
Part II. Motivation and Emotion: What Makes Us Go

Chapter 5 • Drugs, Addiction, and Reward

Psychoactive Drugs

Opiates and Opioids
A Further Look | A New Treatment for Pain: Botox
A Further Look | Government Agencies Act to Curb Overdose Deaths

Depressants
A Further Look | The Auto-Brewery Syndrome

Stimulants
Psychedelic Drugs
Marijuana
A Further Look | Changing Attitudes Toward Marijuana Addiction

The Role of Reward in Addiction
Synaptic Plasticity and Addiction
Treating Drug Addiction
A Further Look | Targeting the Brain to Lessen Drug Withdrawal
The Role of Genes in Addiction

Separating Genetic and Environmental Influences

What Is Inherited?
Implications of Addiction Research
Chapter 6 • Motivation and the Regulation of Internal States

Motivation and Homeostasis

Theoretical Approaches to Motivation
Simple Homeostatic Drives
Hunger: A Complex Drive

Gustation: The Role of Taste
A Further Look | Predator Control Through Learned Taste Aversion

Digestion and the Two Phases of Metabolism
The Hypothalamic Circuitry of Hunger
Signals That Initiate and Terminate Eating
Long-Term Controls
A Further Look | How Nicotine and Marijuana Affect Appetite
Obesity
A Further Look | Diabetes, the Duck-Billed Platypus, and the Cone Snail

The Myths of Obesity
The Contributions of Heredity and Environment
A Further Look | Obesity Alters Your DNA

Obesity and Reduced Metabolism
Treating Obesity
A Further Look | Pets May Provide Protection Against Obesity
Anorexia, Bulimia, and Binge Eating Disorder

Environmental and Genetic Contributions
The Role of Neurotransmitters
Chapter 7 • The Biology of Sex and Gender

Sex as a Form of Motivation

Arousal and Satiation
Hormonal Control of Sexual Behavior
Brain Structures and Neurotransmitters

Odors, Pheromones, and Sexual Attraction
A Further Look | Of Love, Bonding, and Empathy
The Biological Determination of Sex
Chromosomes and Hormones
Prenatal Hormone Influences on Brain and Behavior
Gender-Related Behavioral and Cognitive Differences
Some Demonstrated Male–Female Differences
Origins of Male–Female Differences
A Further Look | GTEx Project Provides New Insight Into the Differences Between the Sexes
Biological Origins of Gender Identity
Transgender
Transgender and the Brain
46,XY Intersex
46,XX Intersex
A Further Look | Sex, Gender, and Sports
Cognitive and Behavioral Effects
Ablatio Penis and Other Natural Experiments
A Further Look | Who Gets to Choose a Child's Sex?
Sexual Orientation
The Social Influence Hypothesis
Genetic and Epigenetic Influences
Prenatal Influences on Brain Structure and Function
Social Implications of the Biological Model
Chapter 8 • Emotion and Health
Emotion and the Nervous System
Autonomic and Muscular Involvement in Emotion
The Emotional Brain
A Further Look | Why Bob Doesn't Jump Out of Airplanes
Stress, Immunity, and Health
Stress as an Adaptive Response
A Further Look | How Puffer Fish Manage Stress

Negative Effects of Stress
Social, Personality, and Genetic Factors
A Further Look | One Aftermath of Disaster Is Stress-Related Brain Damage

Pain as an Adaptive Emotion
Biological Origins of Aggression

The Brain's Role in Aggression
Hormones and Neurotransmitters in Aggression
A Further Look | A Bug That Causes Road Rage?

Heredity and Environment
A Further Look | Neurocriminology, Responsibility, and the Law
Part III. Interacting With the World

Chapter 9 • Hearing and Language

Hearing

The Adequate Stimulus for Hearing
The Auditory Mechanism
Frequency Analysis
Restoring Hearing
A Further Look | Beyond Cochlear Implants

Analyzing Complex Sounds
Locating Sounds
A Further Look | I Hear a Tree Over There
Language

Broca's Area
Wernicke's Area
The Wernicke-Geschwind Model
Reading, Writing, and Their Impairments
Recovery From Aphasia and Lateralization of Language
A Language-Generating Mechanism?
Language in Nonhuman Animals
Neural and Genetic Antecedents
A Further Look | What Do the Gestures of Apes and Humans Have in Common?

Chapter 10 • Vision and Visual Perception

Light and the Visual Apparatus

The Visible Spectrum
The Eye and Its Receptors
Pathways to the Brain
Color Vision

Trichromatic Theory
Opponent Process Theory
A Combined Theory
A Further Look | Restoring Lost Vision

Color Blindness
Form Vision

Contrast Enhancement and Edge Detection
A Further Look | Neural Bases of Visual Illusions

Hubel and Wiesel's Theory
Spatial Frequency Theory
The Perception of Objects, Color, and Movement

The Two Pathways of Visual Analysis
Disorders of Visual Perception
The Problem of Final Integration
A Further Look | When Binding Goes Too Far
Chapter 11 • The Body Senses and Movement

The Body Senses

Proprioception
The Skin Senses
The Vestibular Sense
The Somatosensory Cortex and the Posterior Parietal Cortex
Pain and Its Disorders
A Further Look | Treating Pain in Limbs That Aren't There
Movement

The Muscles

The Spinal Cord
The Brain and Movement
A Further Look | Brain-Computer Interfaces

Disorders of Movement
A Further Look | Deep Brain Stimulation and Parkinson's Disease
Part IV. Complex Behavior

Chapter 12 • Learning and Memory

Learning as the Storage of Memories

Amnesia: The Failure of Storage and Retrieval
A Further Look | The Legacy of H. M.

Mechanisms of Consolidation and Retrieval
Where Memories Are Stored
Two Kinds of Learning
Working Memory
Brain Changes in Learning

Long-Term Potentiation
How LTP Happens
Consolidation and Sleep
Changing Our Memories
A Further Look | Total Recall
Learning Deficiencies and Disorders

Effects of Aging on Memory
Alzheimer's Disease
A Further Look | Alzheimer's in a Dish

Other Dementias
Chapter 13 • Intelligence and Cognitive Functioning

The Nature of Intelligence

What Does "Intelligence" Mean?
The Structure of Intelligence
The Biological Origins of Intelligence

The Brain and Intelligence

Specific Abilities and General Intelligence
A Further Look | We Aren't the Only Tool Users

Heredity and Environment
Deficiencies and Disorders of Intelligence

Effects of Aging on Intelligence
A Further Look | Enhancing Intelligence and Cognitive Performance

Intellectual Disability
Autism Spectrum Disorder
A Further Look | Childhood Vaccines and Autism

Attention-Deficit/Hyperactivity Disorder
Chapter 14 • Psychological Disorders

Schizophrenia

Characteristics of the Disorder
Heredity
Two Types of Schizophrenia Symptoms
The Dopamine Hypothesis
Beyond the Dopamine Hypothesis
A Further Look | Antipsychotics and Their Side Effects

Neurological Anomalies in Schizophrenia
Affective Disorders

Heredity
The Monoamine Hypothesis of Depression
A Further Look | Targeting Drugs to Specific Receptors

Electroconvulsive Therapy
Antidepressants, ECT, and Neural Plasticity
Rhythms and Affective Disorders
Bipolar Disorder and Related Disorders
Neurological Anomalies in Affective Disorders
Suicide
Anxiety, Trauma, and Stress-Related Disorders

Heredity
Generalized Anxiety, Panic Disorder, and Phobia

Posttraumatic Stress Disorder
Anomalies in Brain Functioning
Personality Disorders

Obsessive-Compulsive Disorder
A Further Look | OCD and Mysophobia

OCD-Related Disorders (Grooming and Hoarding)
Borderline Personality Disorder
Chapter 15 • Sleep and Consciousness

Sleep and Dreaming

Circadian Rhythms
Rhythms During Waking and Sleeping
The Functions of Sleep
Sleep, Plasticity, and Memory
Brain Structures of Sleep and Waking
Sleep Disorders
A Further Look | In the Still of the Night

Sleep as a Form of Consciousness
The Neural Bases of Consciousness

Structural and Network Explanations of Consciousness
Awareness
A Further Look | Determining Consciousness When It Counts

Attention
The Sense of Self
Glossary
References
Author Index
Subject Index

PREFACE

A Message From the Authors

> *Anyone who stops learning is old, whether at twenty or eighty. Anyone who keeps learning stays young. The greatest thing in life is to keep your mind young.*
>
> —Henry Ford

Flip through this book and you'll see that its pages are chock-full of facts and applications—just a sampling gleaned from a vast supply that grows too fast for any of us to keep up with and that becomes obsolete just as fast. But sifting through those facts and reporting them is neither the most difficult nor the most important function of a good textbook. A greater challenge is that most students fail to share their instructors' infatuation with learning; perhaps they lack the genes, or the parental role models, or just the idea that learning can be fun. At any rate, they can find a text like this intimidating, and it is the textbook's role to change their minds.

The colorful illustrations, case studies, and research vignettes may capture students' interest, but sparking interest alone is not enough. That's why we've adopted a big-picture approach in writing the text, one that marshals facts into explanations and discards the ones left standing around with nothing to do. When you put facts to work that way, you begin to see students look up and say, "That makes sense," or "I've always wondered about that, but I never thought of it that way," or "Now I understand what was going on with Uncle Edgar."

We believe education has the capacity to make a person healthy, happy, and productive, and it makes a society strong. Education realizes that promise when it leads people to inquire and to question —when they *learn how to learn*. When 45% of the public believes in ghosts, and politics has become a game played by shouting the loudest or telling the most convincing lie, education more than ever

needs to teach young people to ask, “Where is the evidence?” and “Is that the only reasonable interpretation?”

To those who would teach and those who would learn, this book is for you.

TO THE STUDENT

Brain & Behavior is our attempt to reach out to students, to beckon them into the fascinating world of behavioral neuroscience. These are exceptionally exciting times, comparable in many ways to the renaissance that thrust Europe from the Middle Ages into the modern world. According to the American neurologist Stanley B. Prusiner (n.d.),

> neuroscience is by far the most exciting branch of science because the brain is the most fascinating object in the universe. Every human brain is different—the brain makes each human unique and defines who he or she is.

We know of no scientific discipline with greater potential to answer the burning questions about ourselves than behavioral neuroscience. We hope this textbook will convey that kind of excitement as you read about discoveries that will revolutionize our understanding of what it means to be human, and how we got to where we are.

We want you to succeed in this course, but, more than that, we want you to learn more than you ever imagined you could and to go away with a new appreciation for the promise of behavioral neuroscience. So we have a few tips we want to pass along. First, try to sit near the front of the class, because those students usually get the best grades. That is probably because they stay more engaged and are encouraged to ask more questions, but to ask good questions, you should always read the text before you go to class. And so that you’ll know where you’re going before you begin to read, take a look at “After reading this chapter, you will be able to,” then skim the chapter subheadings and read the summary at the end of the chapter.

Some special tips if you are using this text for an online course: First, make sure you ask questions of your instructor as you go through the material, and attend their virtual office hours! An online course is much more challenging—you are responsible for keeping up with the material on your own without the in-person reminders you'd normally get from a physical class. And when answering questions, make sure you document where you got your information; it is all too easy to simply copy and paste information without properly citing your sources. Finally, get into a study group with your fellow students. Not everybody understands the material with a single read-through, so discussing the content and exercises with your fellow students can help all of you grasp the complex concepts of behavioral neuroscience.

As you read, pay special attention to the text in blue; these are definitions of the most important terms, which are defined again in the glossary at the end of the book. Answer the Concept Check questions at the end of each section and the For Further Thought questions at the end of the chapter, and be sure to check your knowledge with Test Your Understanding. Then don't forget to look up some of the books and articles in For Further Reading; we selected these not only to increase your understanding of a particular topic but to be fun as well! Finally, the Student Resources site, at **edge.sagepub.com/garrett6e**, will provide you with a wealth of additional help. If you do all these things, you won't just do better in this course; you will leave saying, "I really got something out of that class!" And when it's time to take the GRE (or MCAT or VCAT), or talk to your doctor, or interview for a biomedical job, or simply read the Science section of the *New York Times*, you'll be using the knowledge you gained in this text.

We wrote *Brain & Behavior* with you in mind, so we hope you will let us know where we have done things right and, especially, where we have not. We wish you the satisfaction of discovery and knowledge as you read what we have written *for you*.

TO THE INSTRUCTOR

A good textbook is all about teaching, but there is no teaching if there is no learning. Over the years, our students have taught us a great deal about what they need to help them learn. For one thing, we have realized how important it is for students to build on their

knowledge throughout the course, so we have made several changes from the organization of other texts. First, the chapter on neuronal physiology precedes the chapter on the nervous system, because we believe that you can't begin to understand the brain until you know how its neurons work. And we reverse the usual order of the vision and audition chapters, because audition provides a friendlier context for introducing the basic principles of sensation and perception. The chapters on addiction, motivation, emotion, and sex follow the introduction to neurophysiology; this was done to build student motivation before tackling sensation and perception. Perhaps more significantly, some topics have been moved around among chapters so that they can be developed in a more behaviorally meaningful context. So we discuss language along with audition, the body senses with the mechanisms of movement, the sense of taste in the context of feeding behavior, and olfaction in conjunction with sexual behavior. Most unique, though, is the inclusion of a chapter on the biology of intelligence and another on consciousness. The latter is a full treatment of recent developments in the field, rather than being limited to the usual topics of sleep and split-brain behavior. These two chapters strongly reinforce the theme that behavioral neuroscience is personally relevant and capable of addressing important questions.

Brain & Behavior has several features that will motivate students to learn and encourage them to take an active role in their learning. It engages the student with interest-grabbing opening vignettes, illustrative case studies, A Further Look features that take an intriguing step beyond the chapter content, and a Concept Check at the end of each section that serves as a reminder of the important ideas. At the end of each chapter, In Perspective emphasizes the importance and implications of what the student has just read, a summary helps organize that information, and Test Your Understanding questions assess the student's comprehension. For Further Reading suggestions guide the student in exploring the chapter's topics more fully. We have found over the years that students who use the study aids in a class are also the best performers in the course.

NEW IN THE SIXTH EDITION

When we published the fifth edition 3 years ago, we called it "the most ambitious revision of *Brain & Behavior* since the second"; the

sixth rivals both of those. We consulted literally thousands of research articles and selected 516 of them in our effort to make sure *Brain & Behavior* has the most up-to-date coverage possible. To supplement this new information, we revised or replaced 70 illustrations and added a dozen new or revised animations. We replaced the three boxed features of previous editions with A Further Look and added content ranging from the challenge of regulating gene editing in the age of CRISPR (think CRISPR baby scandal and do-it-yourself kits), to communicative gestures humans share with apes, to a description of how actin motors help neurons inch forward during migration by "walking" microtubules along other microtubules.

As was the case in the fifth edition, genetics and neural connectivity dominate behavioral neuroscience research. As we point out in Chapter 14, fast, inexpensive genome-wide association studies have enabled hypothesis-free "gene snooping" that is turning up numerous gene locations but at the expense of requiring samples of 10,000 subjects to provide statistical protection against spurious "hits." Although hypoconnectivity has long been accepted as characteristic of many disorders, we are also finding hyperconnectivity in the same individuals, which is usually associated with more severe symptoms. However, in children with autism who had interhemispheric underconnectivity between the auditory areas, those with increased connections between the auditory cortex and the thalamus had fewer deficits in language, communication, and social behaviors.

Communication with the student has been foremost in the 18-year history of *Brain & Behavior*, and to that end, we have done extensive rewriting in this edition. Examples include the discussion of osmotic and hypovolemic thirst in Chapter 6 and the section on risk taking and decision making in Chapter 8. In addition, we added a new section in Chapter 5, The Hypothalamic Circuitry of Hunger, to better organize that information. As a part of improving communication, we have also tried to be especially mindful of language that might be offensive to our readers as we discuss gender-related issues and describe individuals with psychological disorders. We have always given special attention to applications of neuroscientific knowledge, particularly in the form of treatments. Three new experimental treatments, for example, attack addiction by interfering with drug-related memories—by blocking acetylcholine receptors, applying transcranial magnetic stimulation, or blocking reconsolidation with a single dose of ketamine during recall of alcohol-related memories.

The prospects of gaining approval for three Alzheimer's drugs were revived after they appeared to fail in Phase 3 trials—when patients chose to continue the drug after one study was scrubbed and in two others when improvement was noted only in the control subjects, who were given minute "placebo" dosages.

With more than 500 added references, you can expect to see a number of new research findings and fresh ideas. A few highlights:

- There is new evidence that fathers who smoke pass gene mutations to their offspring, along with an increased risk of birth defects and childhood cancers and reduced fertility in the male offspring.
- Although the majority of epigenetic changes in obese individuals appear to be the result of obesity, brain characteristics such as cortical thinning are likely a hereditary component of obesity rather than a consequence of it.
- We've pointed out before that the Wernicke-Geschwind model is too simple; now we've added a new section, Beyond the Wernicke-Geschwind Model, that describes current knowledge.
- A breakthrough in stem cell therapy has enabled blind individuals to read at 60 to 80 words per minute.
- The idea presented in the fifth edition that infection rate accounts for national differences in intelligence is bolstered by two findings: IQ is negatively related to the number of hospitalizations for infection, and the immune response impairs brain plasticity and learning ability.
- A recently discovered "glymphatic system" transports cerebrospinal fluid among the brain cells during sleep to flush out toxins and debris, such as β-amyloid.

ACKNOWLEDGMENTS

Revising a textbook like *Brain & Behavior* is incredibly hard work, and the sixth edition would not be possible without the help of many

others. Kudos to acquisitions editor Abbie Rickard, content development editor Emma Newsom, and assistant content development editor Sam Rosenberg for their insights, their guidance, and their ability to keep us on schedule (almost). Thanks also to Laureen Gleason for her remarkable copyediting and gentleness in pointing out our many errors, to Ashley Brown for her enthusiasm and great care in managing the animations, and to Elizabeth Cruz for doggedly pursuing permissions for the material in our figures.

Bob has had a number of mentors along the way, to whom he is forever grateful. A few of those special people are Wayne Kilgore, who taught the joys of science along with high school chemistry and physics; Garvin McCain, who introduced him to the satisfactions of research; Roger Kirk, who taught him that anything worth doing is worth doing over and over until it's right; and Ellen Roye and Ouilda Piner, who shared their love of language. These dedicated teachers showed him that learning was his responsibility, and they shaped his life with their unique gifts and quiet enthusiasm. But of all of Bob's supporters, the most important was his late wife, Duejean; love and thanks to her for fond memories and for her patient understanding and her appreciation of how important this project has been to him.

For Gerald, becoming a coauthor on this textbook, which he has used in his classes over the past decade, is an amazing privilege. He hopes that the instructors and students who use this book find that the overall presentation and helpfulness in assisting in the learning process are unchanged from the previous editions. His background in behavioral neuroethology (a mouthful, for sure!) provides a background in understanding the neural bases of behavior. He would like to thank his academic mentors, who have helped him find his way in a complex scientific world: Erich Klinghammer at Wolf Park in Battle Ground, Indiana, sowed the seeds for a love of wolves and understanding behavior in naturalistic settings; Susan Volman at NIDA (formerly The Ohio State University) introduced him to the complexities of behavioral neuroscience through their investigation of how birds learn (and forget) songs at the neural level; and Verner Bingman gave him the opportunity to develop as a scholar and mentor to his students at Bowling Green State University in Ohio. Finally, he would like to thank his colleagues at Rowan University, who provided valuable feedback and discussions on material in their areas of expertise: D. J. Angelone, Thomas Dinzeo, and Alison Krufka. He would also like to thank his family for letting him work on this important textbook: his

wife of almost 30 years, Kerry; his teenage sons, Alexander and Benjamin; and his mother, Carole, who is finally living close to home.

In addition, the following reviewers gave generously of their time and expertise throughout the development of this text; they contributed immensely to the quality of *Brain & Behavior*:

First edition: Susan Anderson, University of South Alabama; Patrizia Curran, University of Massachusetts–Dartmouth; Lloyd Dawe, Cameron University; Tami Eggleston, McKendree College; James Hunsicker, Southwestern Oklahoma State University; Eric Laws, Longwood College; Margaret Letterman, Eastern Connecticut State University; Doug Matthews, University of Memphis; Grant McLaren, Edinboro University of Pennsylvania; Rob Mowrer, Angelo State University; Anna Napoli, University of Redlands; Robert Patterson, Washington State University; Joseph Porter, Virginia Commonwealth University; Jeffrey Stern, University of Michigan–Dearborn; Aurora Torres, University of Alabama in Huntsville; Michael Woodruff, East Tennessee State University; and Phil Zeigler, Hunter College.

Second edition: M. Todd Allen, University of Northern Colorado; Patricia A. Bach, Illinois Institute of Technology; Wayne Brake, University of California–Santa Barbara; Steven I. Dworkin, University of North Carolina; Sean Laraway, San Jose State University; Mindy J. Miserendino, Sacred Heart University; Brady Phelps, South Dakota State University; Susan A. Todd, Bridgewater State College; and Elizabeth Walter, University of Oregon.

Third edition: John A. Agnew, University of Colorado Boulder; Michael A. Bock, American International College; Rachel E. Bowman, Sacred Heart University; Jessica Cail, Pepperdine University; Mary Jo Carnot, Chadron State College; Cheryl A. Frye, The University at Albany–State University of New York; Rebecca L. M. Fuller, Catholic University of America; Cindy Gibson, Washington College; Bennet Givens, The Ohio State University; Robert B. Glassman, Lake Forest College; Gerald E. Hough, Rowan University; Joseph Nuñez, Michigan State University; and Kimberly L. Thomas, University of Central Oklahoma.

Fourth edition: John A. Agnew, University of Colorado Boulder; Ben Allen, University of Pittsburgh; Scott L. Decker, University of South Carolina; Carol L. DeVolder, St. Ambrose University; Jeff Dyche, James Madison University; Cindy Gibson, Washington College;

Deirdre C. Greer, Columbus State University; William Meil, Indiana University of Pennsylvania; Samar Saade Needham, California State University, Long Beach; M. Foster Olive, Arizona State University; Catherine Powers Ozyurt, Bay Path College; Allen Salo, University of Maine at Presque Isle; Justin P. Smith, University of South Dakota; Gretchen Sprow, University of North Carolina at Chapel Hill; and Sandra Trafalis, San Jose State University.

Fifth edition: Kurt T. Choate, Northeastern State University; Andrea L. O. Hebb, Saint Mary's University; Bryant Horowitz, East Los Angeles College, California State University, Northridge, and The Chicago School of Professional Psychology; Dwight J. Kravitz, The George Washington University; and Lorenz S. Neuwirth, SUNY College at Old Westbury.

Sixth edition: Elizabeth Becker, St. Joseph's University; William Collins, Nova Southeastern University; Kelly Curtis, High Point University; Sharon Goyette, Bridgewater State University; Maxine Krengel, University of Massachusetts Boston; Linda Lockwood, Metropolitan State University of Denver; Karen Murphy, Duke University; Jim Paulus, Tabor College; and Leora Yetnikoff, College of Staten Island.

—Bob Garrett and Gerald Hough

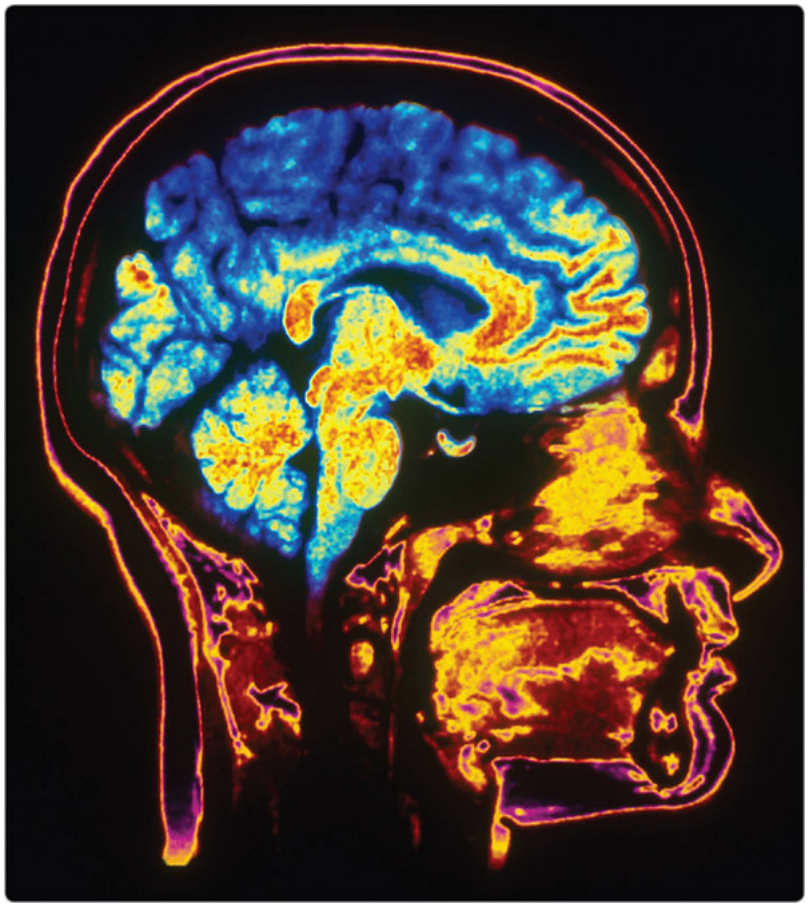
In the electronic edition of the book you have purchased, there are several icons that reference links (videos, journal articles) to additional content. Though the electronic edition links are not live, all content referenced may be accessed at edge.sagepub.com/garrett6e . This URL is referenced at several points throughout your electronic edition.

ABOUT THE AUTHORS

Bob Garrett
is a Visiting Scholar at California Polytechnic State University, San Luis Obispo. He was Professor of Psychology at DePauw University in Greencastle, Indiana, and held several positions there, including Chairperson of the Department of Psychology, Faculty Development Coordinator, and Interim Dean of Academic Affairs. He received his BA from the University of Texas at Arlington and his MA and PhD from Baylor University. He received further training in the Department of Physiology at Baylor University College of Medicine and at the Aeromedical Research Primate Laboratory, Holloman Air Force Base. Bob lives on a 3,200-acre ranch he shares with 48 other families in the hills outside San Luis Obispo. His sons, Geoffrey and Michael, and grandchildren, Evan, Naomi, and Talia, all live nearby.

Gerald (Jerry) Hough
is an Associate Professor of Biological Sciences and Psychology at Rowan University in Glassboro, New Jersey. He received his BS from Purdue University and his MS and PhD from The Ohio State University. He also worked in the lab of Verner Bingman at Bowling Green State University. He has taught undergraduate and graduate courses on anatomy, animal behavior, research methods, psychopharmacology, cognitive neuroscience, physiology, and learning. He is an elected member of the American Ornithologists Union from his work on sparrows, pigeons, and Hawai'ian 'amakihi birds. He has served as the Undergraduate Advising Coordinator for Psychology, as the Chair of the IACUC, in curriculum development for the Cooper Medical School at Rowan University, and Negotiator and Vice President 1 of the American Federation of Teachers Local 2373 at Rowan University. His research focus is in the evolutionary and neural bases of spatial and communication behaviors in birds. Gerald; his wife, Kerry; their two sons; and his mother, Carole, live in lovely southern New Jersey.

1 WHAT IS BEHAVIORAL NEUROSCIENCE?



Scott Camazine/Science Source

The Origins of Behavioral Neuroscience

- Prescientific Psychology and the Mind-Brain Problem
- Descartes and the Physical Model of Behavior
- Helmholtz and the Electrical Brain
- The Localization Issue

Concept Check

Nature and Nurture

- The Genetic Code
- The Human Genome Project
- Heredity: Destiny or Predisposition?

A Further Look | CRISPR: A New Tool to Edit Genes

Concept Check

In Perspective

Chapter Summary

Study Resources

After reading this chapter, you will be able to

1.1 Define the mind-brain problem in behavioral neuroscience.

1.2 Describe the contributions of philosophers and scientists to the development of behavioral neuroscience as a field of study.

1.3 Identify the role of physiologists in the establishment of modern-day behavioral neuroscience.

1.4 Compare the relative contributions of genes and environment in the development of behavioral characteristics.

1.5 Critique the fixed nature of heredity in shaping behavior.

That device you carry in your pocket is a wonder of modern technology. It represents a very recent step in the evolution of long-distance communications, which began with smoke signals and drum beats and progressed through the telegraph, the wireless radio, and the landline telephone.

Mobile telephones appeared in vehicles in 1956, but a handheld mobile was not commercially available until 1983; dubbed the “brick,” it weighed 1.75 pounds (0.79 kilograms) and cost $3,995 (Figure 1.1). Your 4- or 5-ounce phone operates over a vast cellular network to connect you to your friends and family and an estimated 5 billion people all around the world (there are actually more mobile devices on earth than there are people). Assuming you have a smartphone, you have access to many additional people by way of email, text, and video, as well as more than 1.8 billion websites on the Internet. Your phone also allows you to record memories in the form of notes and images, perform calculations, identify a tune or a flower, find your friends, and determine the best route for your road trip.

Figure 1.1 Lead Engineer Martin Cooper With the Motorola DynaTAC 8000X. When the first handheld cellular phone came out in 1984, it cost $4,000 (about $10,000 today), had a battery that took 10 hours to charge, and only had 30 minutes of talk time.

Ted Soqui/Corbis Historical/Getty Images

The brain has many similarities. An iPhone XR has around 7 trillion transistors (Shankland, 2018). The human brain contains about 80 billion neurons, but each of these in turn connects to thousands of others, forming a network of more than 100 trillion synapses (The Human Memory, 2019) where the brain's work is done. One computational neuroscientist estimates that the brain's storage capability rivals that of the Internet; as a psychologist put it, if the brain were a video recorder, it could store 2,500 GB of video information, which would take you about 300 *years* to watch (Reber, 2010). But storage of memories and information is only one of the brain's many tasks. The brain is organized into specialized subnetworks that orchestrate your body's 650 muscles and 206 bones, generate thought and make decisions, perform calculations, keep track of where you are and help you navigate around your world, tell you when and what to drink and eat, and provide your language capability and range of sensory capabilities. Like the cell phone, the brain has evolved over time and across species, but in this case, as its capability has grown, so has its size. Still, all its amazing power is packed into just 3 pounds of tissue that consumes the same amount of energy as a 20-watt light bulb!

Mobile phones came into their own in the last decade of the 20th century, in terms of both their capabilities—such as built-in cameras, Bluetooth connectivity, and augmented reality—and their popularity, indicated by more sales worldwide in 1998 than for cars and PCs combined. The period was also seminal for the awakening field of neuroscience, so much so that in the United States, it was designated as the Decade of the Brain. Planned as an effort to increase public awareness of the benefits of brain research, the Decade of the Brain was also a celebration of past achievements and a sober look at the future. At the threshold of a new millennium, we understood that we had an obligation to expand the horizons of human knowledge

and advance the treatment of neurological diseases, emotional disorders, and addictions that cost the country a trillion dollars per year in care, lost productivity, and crime (Uhl & Grow, 2004). Since then, in the span of your lifetime, we have developed new treatments for depression, identified key genes responsible for the devastation of schizophrenia, developed agents that block addiction to drugs, found ways to slow the memory impairment of Alzheimer's, produced a map of the human genes, and literally peered into the brain itself to watch it work. These achievements seem remarkable for such a brief span of time, but, in fact, they have their roots in a 300-year scientific past and in 22 centuries of thought and inquiry before that. For that reason, we will spend a brief time examining those links to our past.

THE ORIGINS OF BEHAVIORAL NEUROSCIENCE

The term *neuroscience* identifies the subject matter of the investigation rather than the scientist's training. A neuroscientist may be a biologist, a physiologist, an anatomist, a neurologist, a biochemist, a psychologist, a psychiatrist—or even a computer scientist or a philosopher. Psychologists who work in the area of neuroscience specialize in **behavioral neuroscience**, the branch of psychology that studies the relationships between behavior and the body, particularly the brain. (*Behavioral neuroscience* is the more modern term for *biological psychology*; sometimes the term *biopsychology*, *psychobiology*, or *physiological psychology* is also used.) For psychologists, *behavior* has a very broad meaning, which includes not only overt acts but also internal events such as learning, thinking, and emotion. Behavioral neuroscientists attempt to answer questions such as "What changes in the brain when a person learns?" "Why does one person develop depression and another, under similar circumstances, becomes anxious, while another seems unaffected?" "What is the physiological explanation for emotions?" "How do we recognize the face of a friend?" "How does the brain's activity result in consciousness?" Behavioral neuroscientists use a variety of research techniques to answer these questions, as you will see in Chapter 4. Whatever their area of study or their strategy for doing research, behavioral neuroscientists try to go beyond the mechanics of how the brain works to focus on the brain's role in behavior.

? What is behavioral neuroscience, and how does it relate to psychology?

To really appreciate the impressive accomplishments of today's brain researchers, it is useful, perhaps even necessary, to understand the thinking and the work of their predecessors. Contemporary scientists stand on the shoulders of their intellectual ancestors, who made heroic advances with far less information and technology at their disposal than is available to today's undergraduate student.

Writers have pointed out that psychology has a brief history but a long past. What they mean is that thinkers have struggled with the questions of behavior and experience for more than two millennia, but psychology arose as a separate discipline fairly recently; the date most people accept is 1879, when Wilhelm Wundt (Figure 1.2) established the first psychology laboratory in Leipzig, Germany. But biological psychology would not emerge as a separate science until psychologists offered convincing evidence that the biological approach could answer significant questions about behavior. To do so, they would have to come to terms with an old philosophical question about the nature of the mind. Because the question forms a thread that helps us trace the development of behavioral neuroscience, we will orient our discussion around this issue.

Figure 1.2 Wilhelm Wundt (1832–1920).

Weltrundschau zu Reclams Universum 1902

Prescientific Psychology and the Mind-Brain Problem

This issue is usually called “the mind-body problem,” but it is phrased differently here to place the emphasis squarely where it belongs—on the brain. The **mind-brain problem** deals with what the mind is and what its relationship is to the brain. There can be no doubt that the brain is essential to our behavior, but does the mind control the brain, or is it the other way around? Alternatively, are the mind and brain the same thing? How these questions are resolved affects how we ask all the other questions of neuroscience.

At the risk of sounding provocative, we argue that there is no such thing as *mind*. It exists only in the sense that, say, weather exists; weather is a concept used to include rain, wind, humidity, and related phenomena. We talk as if there is *a weather* when we say things like “The weather is interfering with my travel plans.” But no one really thinks that there is *a weather*. Most, though not all, neuroscientists believe that we should think of the mind in the same way; it is simply the collection of things the brain does, such as thinking, sensing, planning, and feeling. But when we think, sense, plan, and feel, we get the compelling impression that there is *a mind* behind it all, guiding what we do and how we interpret our world. Most neuroscientists say this is just an illusion; the sense of mind is nothing more than an awareness of what the brain is doing. Mind, like weather, is just a concept; it is not a *something*; it does not *do* anything.

This position is known as monism, from the Greek *monos*, meaning “alone” or “single.” **Monism** is the idea that the mind and the body consist of the same substance. Idealistic monists believe that everything is nonphysical mind, but most monists take the position that the body and mind and everything else are physical; this view is called **materialistic monism**. The idea that the mind and the brain are separate is known as **dualism**. For most dualists, the body is material and the mind is nonmaterial. Most dualists also believe that the mind influences behavior by interacting with the brain.

? How do monists and dualists disagree on the mind-brain question?

This question did not originate with modern psychology. Ancient Egyptian texts about life after death support a dualistic perspective before two millennia BCE, and the Greek philosophers were debating it in the fifth century BCE (G. Murphy, 1949), when Democritus proposed that everything in the world was made up of atoms (*atomos*, meaning “indivisible”), his term for the smallest particle possible. Even the soul, which included the mind, was made up of atoms, so it, too, was material. Plato and Aristotle, considered the two greatest intellectuals among the ancient Greeks, continued the argument into the fourth century BCE. Plato was a dualist, whereas his monistic student Aristotle joined the body and soul in his attempt to explain memory, emotions, and reasoning.

Defending either position was not easy. The dualists had to explain how a nonphysical mind could influence a physical body, and monists had the task of explaining how the physical brain could account for mental processes such as perception and conscious experience. But the mind was not observable, and even the vaguest understanding of the nervous system was not achieved until the 1800s, so neither side had much ammunition for the fight.

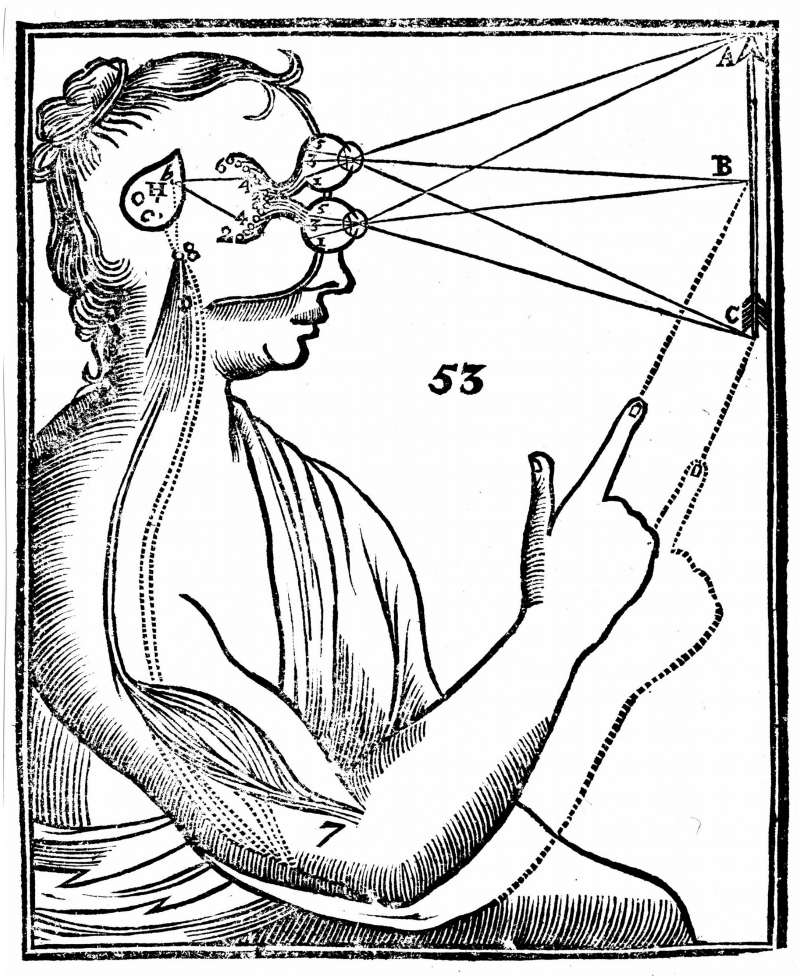
Descartes and the Physical Model of Behavior

Scientists often resort to the use of models to understand whatever they are studying. A **model** is a proposed mechanism for how something works. Sometimes, a model is in the form of a theory, such as Charles Darwin’s explanation that a species developed new capabilities because the capability enhanced the individual’s survival and opportunity to reproduce. Other times, a model is a simpler organism, simulation, or system that scientists study in an attempt to understand a more complex one. For example, researchers have used the rat to model everything from learning to Alzheimer’s disease in humans, and the computer has often been used to simulate models of cognitive processes. Historically, models tended to follow technological advancements in society, especially in early attempts to understand the nervous system. Though as we discuss in Chapter 2 with respect to human-exclusive processes, models will not duplicate the complexity of the human mind.

? What is a model in science, and how is it useful?

In the 17th century, the French philosopher and physiologist René Descartes (Figure 1.3a) used a hydraulic model to explain the brain’s activity (Descartes, 1662/1984). Descartes’s choice of a hydraulic model was influenced by his observation of the statues in the royal gardens at St. Germain. When a visitor stepped on certain tiles, the pressure forced water through tubes to the statues and made them move. Using this model, Descartes then reasoned that nerves were also hollow tubes. The fluid they carried was not water but what he called “animal spirits”; these flowed from the brain and inflated the muscles to produce movement. Sensations, memories, and other mental functions were produced as animal spirits flowed through “pores” in the brain. The animal spirits were pumped through the brain by the pineal gland (Figure 1.3b). Descartes’s choice of the pineal gland (named because it resembled a pine cone) was based on his conclusion that it was at a perfect location to serve this function. Attached just below the two cerebral hemispheres by its flexible stalk, it appeared capable of bending at different angles to direct the flow of animal spirits into critical areas of the brain. It also was, to Descartes, the only part of the brain that was a single organ and not split into left and right sides (Berhouma, 2013). Thus, for Descartes, the pineal gland became the “seat

of the soul," the place where the mind interacted with the body. Although Descartes assigned control to the mind, his unusual emphasis on the physical explanation of behavior foreshadowed the physiological approach that would soon follow.



Description

Figure 1.3 Descartes (1596–1650) and the Hydraulic Model.
Descartes believed that behavior was controlled by animal spirits flowing through the nerves.

iStockphoto.com/traveler1116

Photo 12/Contributor/Getty Images

Descartes lacked an understanding of how the brain and body worked, so he relied on a small amount of anatomical knowledge and a great deal of speculation. His hydraulic model not only represented an important shift in thinking it also illustrates how a model or a theory can lead us astray, at least temporarily. Fortunately, this was the age of the Renaissance, a time not only of artistic expansion and world exploration but also of scientific curiosity. Thinkers began to test their ideas through direct observation and experimental manipulation as the Renaissance gave birth to science. In other words, they adopted the method of **empiricism**, which means that they gathered their information through observation rather than logic, intuition, or other means. Progress was slow, but two critically important principles would emerge as the early scientists ushered in the future.

? What two discoveries furthered the early understanding of the brain?

Helmholtz and the Electrical Brain

In the late 1700s, the Italian physiologist Luigi Galvani showed that he could make a frog's leg muscle twitch by stimulating the attached nerve with electricity, even after the nerve and muscle had been removed from the frog's body. A century later in Germany, Gustav Fritsch and Eduard Hitzig (1870) produced movement in dogs by electrically stimulating their exposed brains. What these scientists showed was that animal spirits were not responsible for movement; instead, the cause was *nerves operated by electricity*! But the German physicist and physiologist Hermann von Helmholtz (Figure 1.4) demonstrated that nerves do not behave like wires conducting electricity. He was able to measure the speed of conduction in nerves, and his calculation of about 90 feet/second (27.4 meters/second) fell far short of the speed of electricity, which travels through wires at the speed of light (186,000 miles/second or 299,000 kilometers/second). It was obvious that researchers were dealing with a biological phenomenon and that the functioning of nerves and of the brain was open to scientific study. Starting from this understanding, Helmholtz's studies of vision and hearing gave "psychologists their first clear idea of what a fully mechanistic 'mind' might look like" (Fancher, 1979, p. 41). As you will see in later chapters, Helmholtz's ideas were so insightful that even today we refer to his theories of vision and hearing as a starting point before describing the current ones.

Figure 1.4 Hermann von Helmholtz (1821–1894).

INTERFOTO / Personalities / Alamy Stock Photo

The Localization Issue

The second important principle to come out of this period—localization—emerged over the first half of the 19th century. **Localization** is the idea that specific areas of the brain carry out specific functions. Fritsch and Hitzig's studies with dogs gave objective confirmation to physicians' more casual observations dating as far back as 17th-century BCE Egypt (Breasted, 1930), but it was two medical case studies that really grabbed the attention of the scientific community. In 1848, a railroad construction foreman named Phineas Gage was injured when a dynamite blast drove an iron tamping rod through his skull and the frontal lobes of his brain (see Chapter 3). Amazingly, he survived with little impairment of his intelligence, memory, speech, or movement. But he became irresponsible and profane and was unable to abide by social conventions (H. Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994). Then, in 1861, the French physician Paul Broca (Figure 1.5) performed an autopsy on the brain of a man who had lost the ability to speak after a stroke. The autopsy showed that damage was limited to an area on the left side of his brain now known as Broca's area (Broca, 1861).

Figure 1.5 Paul Broca (1824–1880).

Wikimedia Commons.

By the mid-1880s, additional observations like these had convinced researchers about localization. But a few brain theorists were already taking the principle of localization too far, and we should be on guard lest we make the same mistake. At the end of the 18th century, when interest in the brain's role in behavior was really heating up, the German anatomist Franz Gall had come up with an extreme and controversial theory of brain localization. According to **phrenology**, each of 35 different "faculties" of emotion and intellect—such as combativeness, inhabitiveness (love of home), calculation, and order—was located in a precise area of the brain (Spurzheim, 1908). Gall and his student Spurzheim determined this by feeling bumps on people's skulls and relating any protuberances to the individual's characteristics (Figure 1.6). Others, such as Karl Lashley (1929), took an equally extreme position at the other end of the spectrum; **equipotentiality** is the idea that the brain functions as an undifferentiated whole. According to this view, the extent of damage, not the location, determines how much function is lost.

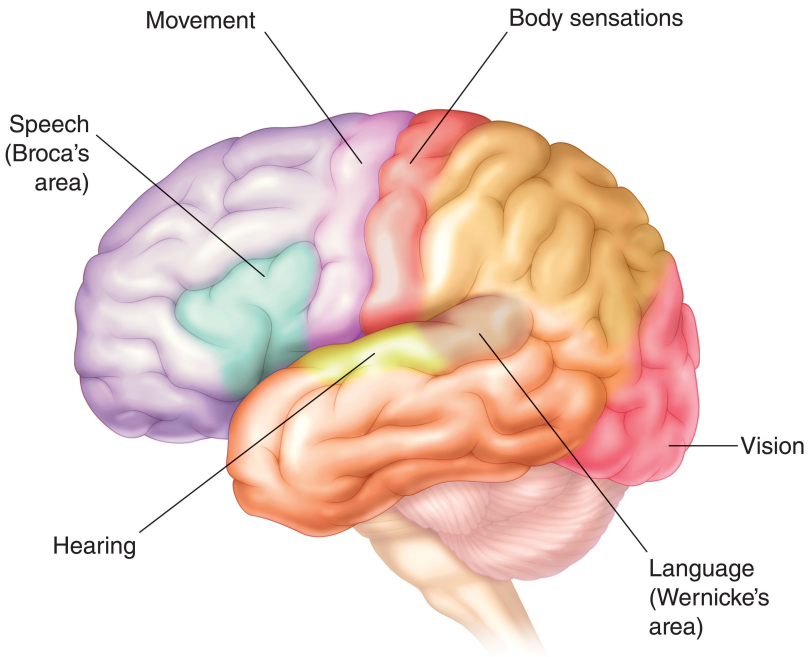
Figure 1.6 A Modern Reproduction of the Phrenologist L. M. Fowler's Map of the Brain.
Phrenologists believed that the psychological characteristics shown here were controlled by the respective brain areas.

Photo-Jope / Shutterstock Images

Obviously, bumps on the skull have nothing to do with the size of the brain structures beneath, and most of the characteristics Gall and Spurzheim identified have no particular meaning at the physiological level. But we also know that the brain is not equipotential. The truth, as is often the case, lies somewhere between these two extremes.

Today's research tells us that functions are as much *distributed* as they are *localized*; behavior results from the interaction of many widespread areas of the brain. In later chapters, you will see examples of cooperative relationships among brain areas in language, visual perception, emotional behavior, motor control, and learning. In fact, you will learn that neuroscientists these days are less likely to ask where a function is

located than to ask how the brain integrates activity from several areas into a single experience or behavior. Nevertheless, the localizationists strengthened the monist position by showing that language, emotion, motor control, and so on are controlled by *relatively* specific locations in the brain (Figure 1.7). This meant that the mind ceased being *the explanation* and became *the phenomenon to be explained*.



Description

Figure 1.7 Some of the Brain's Functional Areas.

Understand that the nature and the role of the mind are still debated in some quarters. For example, some neuroscientists believe that brain research will be unable to explain how a material brain can generate conscious experience and that this will spell the final doom of materialism. These nonmaterial neuroscientists interpret the brain changes that occur during behavior therapy as evidence of the mind changing the brain (J. M. Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996; see Chapter 14). Of course, what material neuroscientists see is the brain changing the brain (Gefter, 2008). Neuroscience has been able to explain a great deal of behavior without any reference to a nonmaterial mind, and as you explore the rest of this text, you will begin to see why most brain scientists would describe themselves as material monists.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- What change in method separated science from philosophy?
- What were the important implications of the discoveries that nerve conduction is electrical and that specific parts of the brain have (more or less) specific functions?
- Where do scientists stand on the localization issue?

NATURE AND NURTURE

A second extremely important issue in understanding the biological bases of behavior is the **nature versus nurture** question, or how important heredity is relative to environmental influences in shaping behavior. Like the mind-brain issue, this is one of the more controversial topics in psychology, at least as far as public opinion is concerned. The arguments are based on emotion and values almost as often as they appeal to evidence and reason. For example, some critics complain that attributing behavior to heredity is just a form of excusing actions for which the person or society should be held accountable. A surprising number of behaviors are turning out to have some degree of hereditary influence, so you will encounter this issue again in later chapters. Because there is so much confusion about heredity, we need to be sure you understand what it means to say that a behavior is hereditary before we go any further.

? How are characteristics inherited?

The Genetic Code

The **gene** is the biological unit that directs cellular processes and transmits inherited characteristics. Most genes are found on the chromosomes, which are located in the nucleus of each cell, but there are also a few genes in structures outside the nucleus, called mitochondria. Each body cell in a human has 46 chromosomes, arranged in 23 pairs (Figure 1.8). Each pair is identifiably distinct from every other pair. This is important, because genes for different functions are found on specific chromosomes. The chromosomes are referred to by number, except for the sex chromosomes; in mammals, females have two X chromosomes, while males typically have an X and a Y chromosome. Notice that the members of a pair of chromosomes are similar to each other, again with the exception that the Y chromosome is much shorter than the X chromosome.

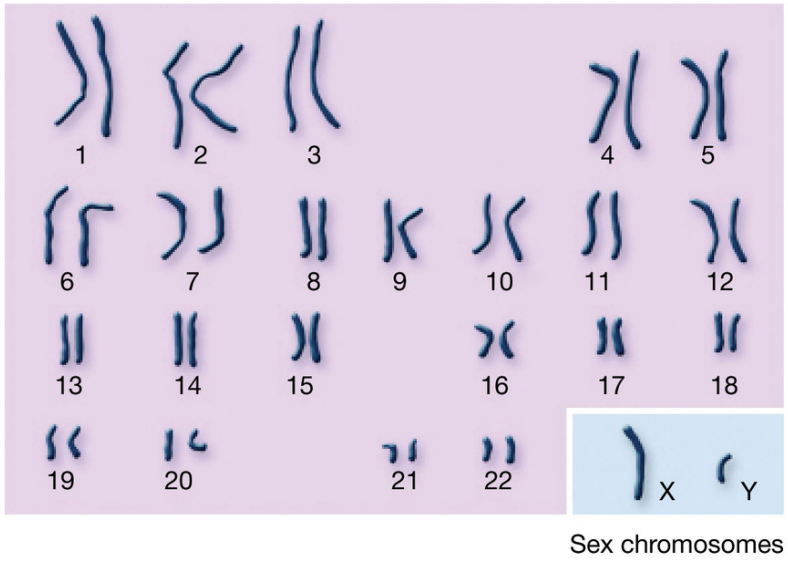


Figure 1.8 A Set of Human Chromosomes.

U.S. National Library of Medicine.

Unlike the body cells, the male's sperm cells and the female's ova (egg cells) each have 23 chromosomes. When these sex cells are formed by the division of their parent cells, the pairs of chromosomes separate, so that each daughter cell receives only one chromosome from each pair. When the sperm enters the ovum during fertilization, the chromosomes of the two cells merge to restore the number to 46. The fertilized egg, or **zygote**, then undergoes rapid cell division and development on its

way to becoming a functioning organism. For the first eight weeks (in humans), the new organism is referred to as an **embryo**, and from then until birth as a **fetus**.

The mystery of how genes carry their genetic instructions began to yield to researchers in 1953, when James Watson and Francis Crick published a proposed structure for the deoxyribonucleic acid that genes are made of. **Deoxyribonucleic acid (DNA)** is a double-stranded chain of chemical molecules that looks like a ladder that has been twisted around itself; this is why DNA is often referred to as a *double helix* (Figure 1.9). Each rung of the ladder is composed of two of the four nucleotides adenine, thymine, guanine, and cytosine (A, T, G, C). The order in which these nucleotides appear on the ladder forms the code that carries all our genetic information. The four-letter alphabet these nucleotides provide is adequate to spell out the instructions for every structure and function in your body.

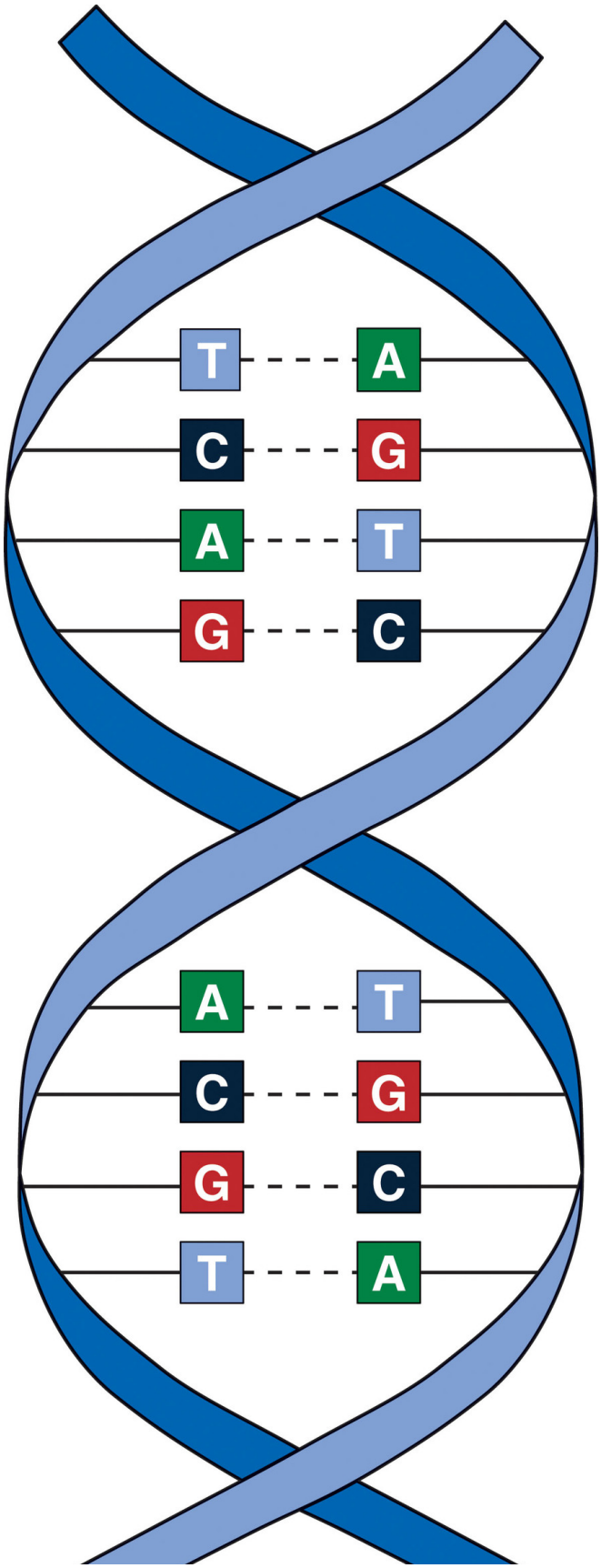
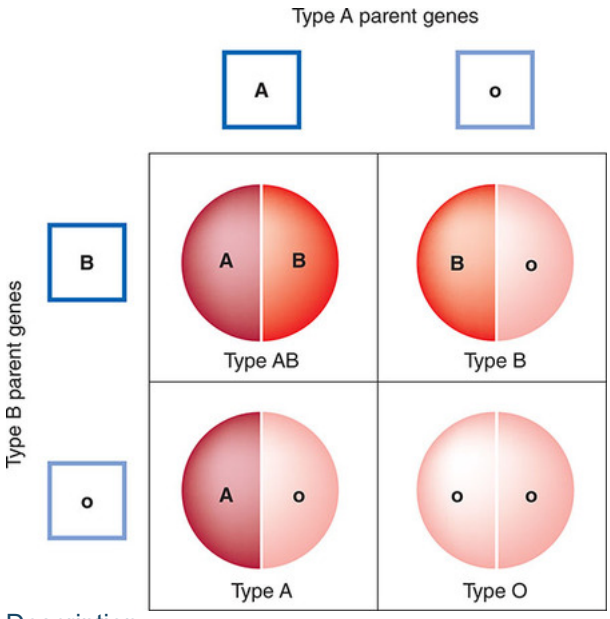

T
A
C
G
A
T
G
C
A
T
C
G
G
C
T
A

Figure 1.9 Structure of a Strand of DNA.

We only partially understand how genes control the development of the body and its activities, as well as how they influence many aspects of behavior. However, we do know that genes exert their influence in a deceptively simple manner: They provide the directions for making proteins. Some of these proteins are used in the construction of the body, and others are enzymes; enzymes act as catalysts, modifying chemical reactions in the body. It is estimated that humans differ among themselves in the sequences of nucleotides that make up our DNA by only about 0.5% (S. Levy et al., 2007); however, you will see throughout this text that this variation leads to enormous differences in development and behavior.

Because all but two of the chromosomes are paired, most genes are as well; a gene on one chromosome is paired with a gene for the same function on the other chromosome. The exception is that the shorter Y chromosome has only 1/25th as many genes as the X chromosome. Although paired genes have the same type of function, their effects often differ; these different versions of a gene are called **alleles**. In some cases, the effects of the two alleles blend to produce a result; for example, a person with the allele for type A blood on one chromosome and the allele for type B blood on the other will have type AB blood.

In other cases, one allele of a gene may be dominant over the other. A **dominant** allele will produce its effect regardless of which allele it is paired with on the other chromosome; a **recessive** allele will have an influence only when it is paired with the same allele. Figure 1.10 illustrates this point. In the example, note that one parent is **heterozygous** for the blood type B allele, which means that the two alleles are different; the other parent is heterozygous for the blood type A allele. The A and B alleles are dominant over the o allele; as a result, each blood type (A, B, AB, or O) has an equal chance (one in four) of occurring in an offspring. Individuals with the same **phenotype** (an observable characteristic such as blood type B) may differ by **genotype** (combinations of alleles such as B and B or B and o). You can see in the figure that type A and B parents have a one in four chance of having a child with different blood types, one of which will be **homozygous** (receiving two identical alleles) for the recessive o allele.



Description

Figure 1.10 Blood Types in the Offspring of Heterozygous Parents.
The small boxes indicate the genes of the two parents; because A and B alleles are dominant over the o allele, the parents' blood types are A and B, respectively. Each offspring receives one allele from each parent; the circles show the four possible

combinations of alleles (genotypes) in the offspring, each of which has an equal chance of occurring. The text under the circles indicates the blood types (phenotypes) of the offspring. Note that type O blood occurs only when the child receives two recessive o alleles.

In the case of unpaired genes on the X chromosome, a recessive gene alone is adequate to produce an effect because it is not opposed by a dominant gene. A characteristic produced by an unpaired gene on the X chromosome is referred to as **X-linked**. With such a large discrepancy in the number of genes on the X and Y chromosomes, you can understand the potential for effects from X linkage. One example is that males are eight times more likely than females to have a deficiency in red-green color vision. See Chapter 10 for more on this deficiency.

? Why do males more often show characteristics that are caused by recessive genes?

Some characteristics—such as blood type and the degenerative brain disorder Huntington's disease—result from a single pair of genes, but many characteristics are determined by several genes; they are **polygenic**. Height is polygenic, and most behavioral characteristics such as intelligence and psychological disorders are also controlled by a large number of genes.

We have known from ancient times that animals could be bred for desirable behavioral characteristics, such as hunting ability or a mild temperament that made them suitable as pets. Darwin helped establish the idea that behavioral traits can be inherited in humans as well, but the idea fell into disfavor as an emphasis on learning as the major influence on behavior became increasingly fashionable. In the 1960s and 1970s, however, the tide of strict environmentalism began to ebb, and the perspective shifted toward a balanced view of the roles of nature and nurture (Plomin, Owen, & McGuffin, 1994). By 1992, the American Psychological Association was able to identify genetics as one of the themes that best represent the present and the future of psychology (Plomin & McClearn, 1993).

Of the behavioral traits that fall under genetic influence, intelligence is the most investigated. Most of the behavioral disorders, including alcoholism and drug addiction, schizophrenia, major mood disorders, and anxiety, are partially hereditary as well (McGue & Bouchard, 1998). The same can be said for some personality characteristics (T. J. Bouchard, 1994) and sexual orientation (J. M. Bailey & Pillard, 1991; J. M. Bailey, Pillard, Neale, & Agyei, 1993; Kirk, Bailey, Dunne, & Martin, 2000).

? What are some of the inheritable behaviors?

However, you should exercise caution in thinking about these genetic effects. Genes do not provide a script or instructions for behavior. They control the production of proteins; the proteins in turn affect the development of brain structures, the production of neurotransmitters and the receptors that respond to them, and the functioning of the glandular system. We will offer specific examples in later chapters, where we will discuss this topic in more depth.

The Human Genome Project

? What is the Human Genome Project, and how successful has it been?

After geneticists have determined that a behavior is influenced by genes, the next step is to discover which genes are involved. The various techniques for identifying genes boil down to determining whether people who share a particular characteristic also share a particular gene or genes that other people don't have. This task is extremely difficult if the researchers don't know where to look, because the amount of DNA is so great. However, the gene search received a tremendous boost in 1990, when a consortium of geneticists at 20 laboratories around the world began a project to identify all the genes in our chromosomes, or the human **genome**.

The goal of the **Human Genome Project** was to map the location of all the genes on the human chromosomes and to determine the genes' codes—that is, the order of bases within each gene. In 2000—just 10 years after the project began—the project group and a private organization simultaneously announced they had produced "rough drafts" (International Human Genome Sequencing Consortium, 2001; Venter et al., 2001); within another 5 years, the entire human genome had been sequenced (Gregory et al., 2006).

But when it comes to gene functioning, there is still more mystery than enlightenment. Only 21,000 of our genes—just 3% of our DNA—have turned out to be protein encoding (ENCODE Project Consortium, 2012). The lowly roundworm has 19,735 protein-coding genes (Hillier, Coulson, & Murray, 2005), so, clearly, the number of genes is not correlated with behavioral complexity. However, the amount of noncoding DNA—which we used to call "junk DNA"—*does* correlate with behavioral complexity (Andolfatto, 2005; Siepel et al., 2005). So what is important about "junk" DNA? Some of it is, in fact, nonfunctional, remnants left behind during evolution. But 80% of the non-protein-coding DNA is biochemically active. Much of it controls the functioning of other genes by altering **gene expression**—the translation of encoded information into the production of proteins (Pennacchio et al., 2006). For example, when a stretch of noncoding DNA known as *HACNS1*—which is unique to humans—is inserted into a mouse embryo, it turns on genes in the "forearm" and "thumb" (Figure 1.11; Prabhakar et al., 2008). DNA taken from the same area in chimpanzees and rhesus monkeys does not have that effect. The researchers speculate that the genes that *HACNS1* turns on led to the evolutionarily important dexterity of the human thumb.

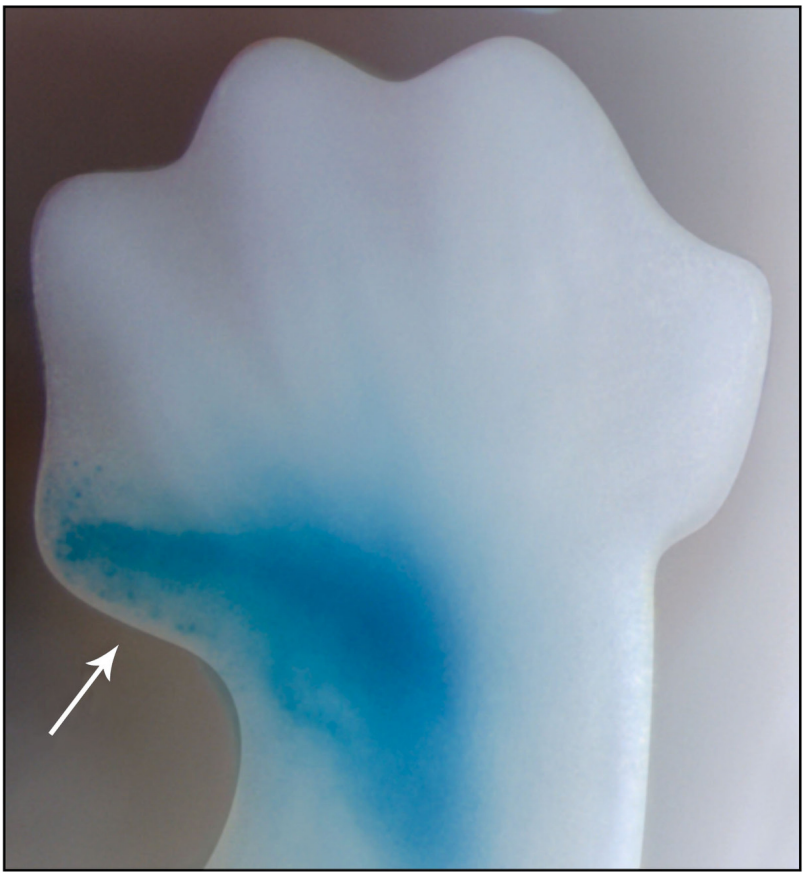


Figure 1.11 Human Junk DNA Turns on Genes in a Mouse Embryo's Paw.
To determine where the DNA was having an effect, it was paired with a gene that produces a blue protein when activated. The blue area indicates that *HACNS1* is targeting genes in the area analogous to the human thumb.

From “Human-specific Gain of Function in a Developmental Enhancer,” by S. Prabhakar et al, *Science*, 321, p. 1348. Reprinted with permission from AAAS.

? Do genes lock a person into a particular outcome in life?

A second question is what the genes do. The gene map doesn’t answer that question, but it does make it easier to find the genes responsible for a particular disorder or behavior. For example, when geneticists were searching for the gene that causes Huntington’s disease in the early 1980s, they found that most of the affected individuals in a large extended family shared a couple of previously identified genes with known locations on chromosome 4, whereas the disease-free family members didn’t. This meant that the Huntington’s gene was on chromosome 4 and near these two *marker* genes (Gusella et al., 1983). Actually finding the Huntington’s gene still took another 10 years; now the gene map is dramatically reducing the time required to identify genes.

Identifying the genes and their functions will improve our understanding of human behavior and psychological as well as medical disorders. We will be able to treat disorders genetically, counsel vulnerable individuals about preventive measures, and determine whether a patient will benefit from a drug or have an adverse reaction, thus eliminating delays from trying one treatment after another.

Heredity: Destiny or Predisposition?

To many people, the idea that several, if not most, of their behavioral characteristics are hereditary implies that they are clones of their parents and their future is engraved in stone by their genes. This is neither a popular nor a comfortable view, and it creates considerable resistance to the concept of behavioral genetics. The view is also misleading; a hallmark of genetic influence is actually *diversity*.

Genes and Individuality

Although family members do tend to be similar to each other, children share only half of their genes with each of their parents or with each other. A sex cell receives a random half of the parent’s chromosomes; as a result, a parent can produce 2^{23}, or 8 million, different combinations of chromosomes. Add to this the uncertainty of which sperm will unite with which egg, and the number of genetic combinations that can be passed on to offspring rises to 60 or 70 trillion! So sexual reproduction increases individuality in spite of the inheritability of traits. This variability powers what Darwin (Figure 1.12) called **natural selection**, which means that those whose genes endow them with more adaptive capabilities are more likely to survive and transmit their genes to more offspring (Darwin, 1859).

Figure 1.12 Charles Darwin (1809–1882).

From Origins, Richard Leakey and Roger Lewin.

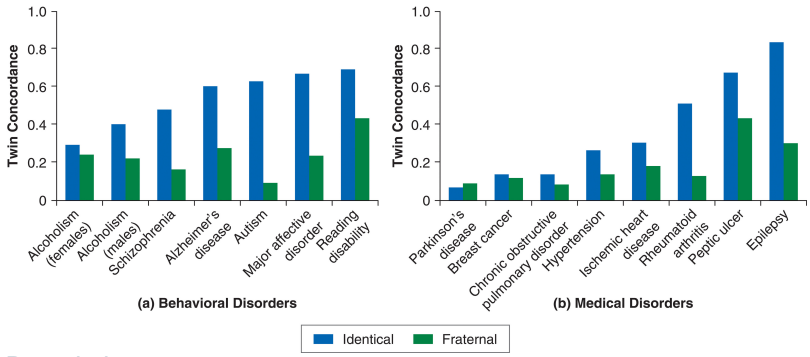
The effects of the genes themselves are not rigid; they can be variable over time and circumstances. Genes are turned on and turned off, or their activity is upregulated and downregulated, so that they produce more or less of their proteins or different proteins at different times. If the activity of genes were constant, there would be no smoothly flowing sequence of developmental changes from conception to adulthood. A large number of genes change their functioning late in life, apparently accounting for many of the changes common to aging (Ly, Lockhart, Lerner, & Schultz, 2000), as well as the onset of diseases such as Alzheimer's (Breitner, Folstein, & Murphy, 1986). The functioning of some genes is even controlled by experience, which explains some of the changes in the brain that constitute learning (C. H. Bailey, Bartsch, & Kandel, 1996). For the past quarter century, researchers have puzzled over why humans are so different from chimpanzees, our closest relatives, considering that 95% to 98% of our DNA sequences are identical (R. J. Britten, 2002; M.-C. King & Wilson, 1975). Part of the answer appears to be that we differ more dramatically in which genes are *expressed*—actually producing proteins—in the brain (Enard et al., 2002).

Genes also have varying degrees of effects. Some determine the person's characteristics, whereas others only influence them. A person with the mutant form of

the *huntingtin* gene *will* develop Huntington's disease, but most behavioral traits depend on many genes. For instance, a single gene will account for only a slight increase in intelligence or in the risk for schizophrenia. The idea of risk raises the issue of vulnerability and returns us to our original question, the relative importance of heredity and environment.

Heredity, Environment, and Vulnerability

To assess the relative contributions of heredity and environment, we need to be able to quantify the two influences. **Heritability** is the percentage of the variation in a characteristic that can be attributed to genetic factors. There are various ways of estimating heritability of a characteristic. One technique involves a comparison of how often identical twins share the characteristic with how often fraternal twins share the characteristic. The reason for this comparison is that identical twins develop from a single egg and therefore have the same genes, while fraternal twins develop from separate eggs and share just 50% of their genes, like nontwin siblings. Heritability estimates are around 50% for intelligence (Devlin, Daniels, & Roeder, 1997), which means that about half of the population's differences in intelligence are due to heredity. Heritability has been estimated at 60% to 90% for schizophrenia (Tsuang, Gilbertson, & Faraone, 1991) and 40% to 50% for personality characteristics and occupational interests (Plomin et al., 1994). By way of comparison, the genetic influence on behavioral characteristics is typically stronger than it is for common medical disorders, as Figure 1.13 shows (Plomin et al., 1994).



Description

Figure 1.13 Twin Studies of Behavioral and Medical Disorders.
The concordance of (a) behavioral disorders and (b) medical disorders in identical and fraternal twins. Concordance is the proportion of twin pairs in which both twins have the disorder. Note the greater concordance in identical twins and the generally higher concordance for behavioral disorders than for medical disorders.

From "The Genetic Basis of Complex Human Behavior," by R. Plomin, M. J. Owen, and P. McGuffin, *Science*, 264, p. 1734. © 1994 American Association for the Advancement of Science. Reprinted with permission from AAAS.

Because about half of the differences in behavioral characteristics among people are attributable to heredity, approximately half are due to environmental influences. Keep in mind that heritability is not an absolute measure but tells us the proportion of variability that is due to genetic influence; the measure depends on the environmental circumstances of the group we're looking at as much as its genetic characteristics. For example, adoption studies tend to overestimate the heritability of intelligence, because adopting parents are disproportionately from the middle class. Because the children's adoptive environments are unusually similar, environmental influence will be lower and heritability higher than in the general population (McGue & Bouchard, 1998). Similarly, heritability will appear to be lower if we look only at a group of closely related individuals.

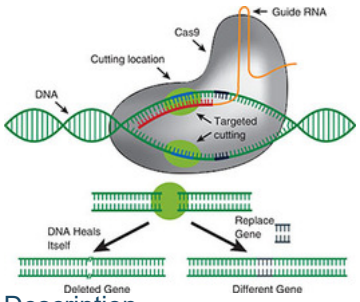
Researchers caution us that “we inherit dispositions, not destinies” (R. J. Rose, 1995, p. 648). This is because the influence of genes is only partial. This idea is formalized in the vulnerability model, which has been applied to disorders such as schizophrenia (Zubin & Spring, 1977). **Vulnerability** means that genes contribute a predisposition for a disorder, which may or may not exceed the threshold required to produce the disorder; environmental challenges such as neglect or emotional trauma may combine with a person’s hereditary susceptibility to exceed that threshold. The general concept applies to behavior and abilities as well, though we wouldn’t use the term *vulnerability* in those contexts. For example, the combination of genes a person receives determines a broad range for the person’s potential intelligence; environmental influences then will determine where in that range the person’s capability will fall. Psychologists no longer talk about heredity versus environment, as if the two are competing with each other for importance. Both are required, and they work together to make us what we are. As an earlier psychologist put it, “to ask whether heredity or environment is more important to life is like asking whether fuel or oxygen is more necessary for making a fire” (Woodworth, 1941, p. 1).

? What do we mean by “genetic predisposition”?

With an increasing understanding of genetics, we are now in the position to change our very being. This kind of capability carries with it a tremendous responsibility. The knowledge of our genetic makeup and the ready availability of genetic testing through companies such as AncestryDNA and 23andMe raise the question of whether it is better for a person to know about a risk that may never materialize, such as susceptibility to Alzheimer’s disease. In addition, many people worry that the ability to do genetic testing on our unborn children means that some parents will choose to abort a fetus because it has genes for a trait they consider undesirable (see A Further Look for more about genetic editing of fetal genes). Our ability to plumb the depths of the brain and of the genome is increasing faster than our grasp of either its implications or how to resolve the ethical questions that will arise. We will consider some of the ethical issues of genetic research in Chapter 4.

A Further Look:

CRISPR: A New Tool to Edit Genes



Description

As we gain an increased understanding of the role, timing, and location of gene actions through efforts such as the Human Genome Project, it is only a matter of time before we will be routinely replacing defective genes in humans with healthy, functioning ones. Replacing or repairing a gene requires three key procedures at the DNA level: (1) identifying key genetic sequences that indicate the start and end of the defective DNA, (2) developing enzymes that can remove the DNA from the genome while leaving the rest of the genetic material intact, and, in some cases, (3) inserting an alternative form of DNA into the genome.

CRISPR stands for *clustered regularly interspaced short palindromic repeats*, which were discovered in bacteria. These repeats are fragments of previous viral infections that the bacterial cell uses to recognize and destroy similar invading viruses. Scientists employ various CRISPR-associated (Cas) proteins, which use an RNA

sequence generated by the scientist as a guide to recognize DNA to be removed; the enzyme then acts like molecular scissors, cutting the ends of the DNA. The cell then patches the break or inserts replacement DNA carried by the Cas enzyme. This technology has the power to revolutionize our understanding of the genetic effects on physiology, behavior, and cognition, as well as to treat genetic diseases.

Though CRISPR is still in its infancy, its early successes have raised fears that this technique will eventually be used for editing human traits and creating designer babies. This fear was heightened in November 2018, when the Chinese scientist He Jiankui admitted that he had edited the genomes of two female embryos in an attempt to make them immune to HIV infection (Marchione, 2018). HIV viruses require the CCR5 receptor to enter white blood cells, and Dr. He was trying to replace the normal receptor gene with the gene for the CCR5 delta 32 receptor, which is HIV resistant. Although the technique was unsuccessful (the girls have one normal and one resistant gene, leaving them susceptible to HIV infection), the use of CRISPR technology on human embryos was universally condemned, and Dr. He was sentenced to 3 years in jail (Normile, 2019).

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- Why is it inappropriate to ask whether heredity or environment is more important for behavior?
- When we say that a person inherits a certain personality characteristic, what do we really mean?
- Explain how two parents who have the same characteristic produce children who are different from them in that characteristic. Use appropriate terminology.
- Explain how genes influence behavior.

IN PERSPECTIVE

In the first issue of the journal *Nature Neuroscience*, the editors observed that brain science still has a “frontier” feel to it. The excitement of exploration is real and tangible, and the discoveries and accomplishments are remarkable for such a young discipline. The successes come from many sources: the genius of our intellectual ancestors, the development of new technologies, the adoption of empiricism, and, we believe, a coming to terms with the concept of the mind. Evidence of all these influences will be apparent in the following chapters.

Behavioral neuroscience still has a long way to go. For all our successes, we do not fully understand what causes schizophrenia, exactly how the brain is changed by learning, or why some people are more intelligent than others. The 1990s was declared the Decade of the Brain; Torsten Wiesel (whose landmark research in vision you will read about later) scoffed at the idea of dedicating a decade to the brain as “foolish. … We need at least a century, maybe even a millennium” (as cited in Horgan, 1999, p. 18). As you read the rest of this book, keep in mind that you are on the threshold of that century’s journey, that millennium of discovery.

Chapter Summary

The Origins of Behavioral Neuroscience

- Behavioral neuroscience (or biopsychology) developed out of physiology and philosophy as early psychologists adopted empiricism.
- Most psychologists and neuroscientists treat the mind as a product of the brain, believing that mental activity can be explained in terms of the brain's functions.
- Localization describes brain functioning better than equipotentiality, but a brain process is more likely to be carried out by a network of structures than by a single structure.

Nature and Nurture

- We are learning that a number of behaviors are genetically influenced. One does not inherit a behavior itself, but genes influence structure and function in the brain and body in a way that influences behavior.
- Behavior is a product of both genes and environment. In many cases, genes produce a predisposition, and environment further determines the outcome.
- With the knowledge of the genome map, we stand on the threshold of unbelievable opportunity for identifying causes of behavior and diseases, but we face daunting ethical challenges as well.

Study Resources

For Further Thought

- Why, in the view of most neuroscientists, is materialistic monism the more productive approach for understanding the functions of the mind? What will be the best test of the correctness of this approach?
- Scientists were working just as hard on the problems of the brain a half century ago as they are now. Why were the dramatic discoveries of recent years not made then?
- What are the implications of knowing what all the genes do and of being able to do a scan that will reveal which genes an individual has?
- If you were told that you had a gene that made it 50% likely that you would develop a certain disease later in life, what could you do with that knowledge?

Test Your Understanding

1. How would a monist and a dualist pursue the study of behavioral neuroscience differently?
2. What was the impact of the early electrical stimulation studies and the evidence that specific parts of the brain were responsible for specific behaviors?

3. The allele for type B blood is, like the one for type A, dominant over the allele for type O. Make a matrix like the one in Figure 1.10 to show the genotypes and phenotypes of the offspring of an AO parent and a BO parent.
4. A person has a gene that is linked with a disease but does not have the disease. We mentioned three reasons why this could occur; describe two of them.
5. Discuss the interaction between heredity and environment in influencing behavior, including the concept of vulnerability.

Select the best answer:

1. The idea that the mind and brain are both physical is known as
    1. idealistic monism.
    2. materialistic monism.
    3. idealistic dualism.
    4. materialistic dualism.
2. A model is
    1. an organism or a system used to understand a more complex one.
    2. a hypothesis about the outcome of a study.
    3. an analogy, not intended to be entirely realistic.
    4. a plan for investigating a phenomenon.
3. Descartes's most important contribution was in
    1. increasing knowledge of brain anatomy.
    2. suggesting the physical control of behavior.
    3. emphasizing the importance of nerves.
    4. explaining how movement is produced.
4. Helmholtz showed that
    1. nerves are not like electrical wires because they conduct too slowly.
    2. nerves operate electrically.
    3. nerves do not conduct animal spirits.
    4. language, emotion, movement, and so on depend on the activity of nerves.
5. In the mid-1800s, studies of brain-damaged patients convinced researchers that
    1. the brain's activity was electrical.
    2. the mind was not located in the brain.
    3. behaviors originated in specific parts of the brain.
    4. the pineal gland could not serve the role Descartes described.
6. Localization means that
    1. specific functions are found in specific parts of the brain.
    2. the most sophisticated functions are located in the highest parts of the brain.
    3. any part of the brain can take over other functions after damage.
    4. brain functions are located in widespread networks.
7. X-linked characteristics affect males more than females because
    1. the X chromosome is shorter than the Y chromosome.
    2. unlike males, females have only one X chromosome.
    3. the responsible gene is not paired with another gene on the Y chromosome.
    4. the male internal environment exaggerates effects of the genes.
8. Two parents are heterozygous for a dominant characteristic. They can produce a child with the recessive characteristic
    1. if the child receives a dominant gene and a recessive gene.
    2. if the child receives two recessive genes.
    3. if the child receives two dominant genes.
    4. under no circumstance.
9. The Human Genome Project has
    1. counted the number of human genes.
    2. made a map of the human genes.
    3. determined the functions of most genes.
    4. cloned most of the human genes.
10. Heritability is greatest for
    1. intelligence.
    2. occupational interest.
    3. personality.
    4. schizophrenia.
11. If we all had identical genes, the estimated heritability for a characteristic would be

1. 0%.
2. 50%.
3. 100%.
4. impossible to determine.

Answers:

1. b, 2. a, 3. b, 4. a, 5. c, 6. a, 7. c, 8. b, 9. b, 10. d, 11. a.

For More Information

The following journals are major sources of neuroscience articles (those that are not *open* access may require a subscription or university access). These may be of use to you as you progress through the textbook and your scholarly pursuits in behavioral neuroscience:

Brain and Behavior (open access)

Brain, Behavior, and Evolution

Frontiers in Neuroscience (open access; also see related journals under “18 Sections”)

Journal of Neuroscience

Nature

Nature Neuroscience

Nature Reviews Neuroscience

New Scientist (for the general reader)

PLoS Biology and ***PLoS Genetics*** (open access)

Scientific American Mind (for the general reader)

The Scientist (for the general reader)

Trends in Neurosciences

General information sites:

BrainFacts (various topics in neuroscience)

Brain in the News (neuroscience news from media sources)

The Human Brain (a collection of brain-related articles published in the magazine *New Scientist*)

Neuroguide (a small but growing offering of resources)

Science Daily (latest developments in science; see “Mind & Brain” and “Health & Medicine”)

For Further Reading

1. “The Emergence of Modern Neuroscience: Some Implications for Neurology and Psychiatry,” by W. Maxwell Cowan, Donald H. Harter, and Eric R. Kandel (*Annual*

Review of Neuroscience, 2000, *23*, 343–391), describes the emergence of neuroscience as a separate discipline in the 1950s and 1960s and describes some of its important accomplishments in understanding disorders.
2. Neuroscientist Michael Gazzaniga calls Mitchell Glickstein's *Neuroscience: A Historical Introduction* (MIT Press, 2014) "authoritative, highly readable, wonderfully illustrated, and just plain interesting."
3. *The Scientific American Brave New Brain*, by Judith Horstman (Jossey-Bass, 2010), describes how today's scientific breakthroughs will in the future help the blind see and help the deaf hear, allow our brains to repair and improve themselves, help us postpone the mental ravages of aging, and give the paralyzed control of prosthetic devices and machinery through brain waves.
4. *Behavioral Genetics*, by Valerie Knopik, Jenae Neiderhiser, John DeFries, and Robert Plomin (Worth, 2017, 7th ed.), is a textbook on that topic; another text, *Evolutionary Psychology*, by William Ray (SAGE, 2013), takes a neuroscience approach to the evolution of behavior.
5. "Tweaking the Genetics of Behavior," by Dean Hamer (*Scientific American*, April 1999, 62–67), is a fanciful but thought-provoking story about a female couple in 2050 who have decided to have a child cloned and the decisions available to them for determining their baby's sex and her physical and psychological characteristics through genetic manipulation.

Key Terms

allele 9

behavioral neuroscience 2

deoxyribonucleic acid (DNA) 8

dominant 9

dualism 4

embryo 8

empiricism 5

equipotentiality 6

fetus 8

gene 8

gene expression 11

genome 11

genotype 9

heritability 12

heterozygous 9

homozygous 9

Human Genome Project 11

localization 6

materialistic monism 4

mind-brain problem 3

model 4

monism 3

natural selection 12

nature versus nurture 8

phenotype 9

phrenology 6

polygenic 9

recessive 9

vulnerability 13

X-linked 9

zygote 8

Descriptions of Images and Figures

Back to Figure

The illustration shows a person looking at an upright arrow directly in front of the eyes. The top of the arrow is labeled A, the center is labeled B, and the bottom is labeled C. A ray from each location on the arrow reaches the eyeballs. The person first points at location C, and then raises the forearm to point at location B. The nerves of the eye and the arm are controlled by the fluid released by a pinecone-shaped gland in the brain.

Back to Figure

The locations of the functional areas on the brain are as follows:

- Movement: Center of the brain at the top.
- Body sensations: Center of the brain at the top, posterior to the region for movement.
- Speech or Broca’s area: Center of the brain, toward its anterior side.
- Hearing: Center of the brain.
- Language or Wernicke’s area: Center of the brain, posterior to the region for hearing.
- Vision: Back of the brain.

Back to Figure

The genes of the parent with blood type A consists of two alleles: A and o. The genes of the parent with blood type B consists of two alleles: B and o. The blood type of their offspring is tabulated below.

Back to Figure

In both graphs, the horizontal axis lists disorders, and the vertical axis is labeled twin concordance, ranging from 0 to 1.0, in increments of 0.2. All data are approximate.

a. Behavioral disorders: The data from the table are tabulated below.

b. Medical disorders: The data from the table are tabulated below.
Back to image

A D N A passes through a protein labeled C a s 9. Inside the protein, the D N A splits and targeted cutting of the gene takes place at specific cutting locations on the strand. The proteins in the guide R N A, present in C a s 9, pair with the proteins of one of the D N A strands. The cut D N A either heals itself, resulting in a deleted gene, or replaces the gene, resulting in a different gene.

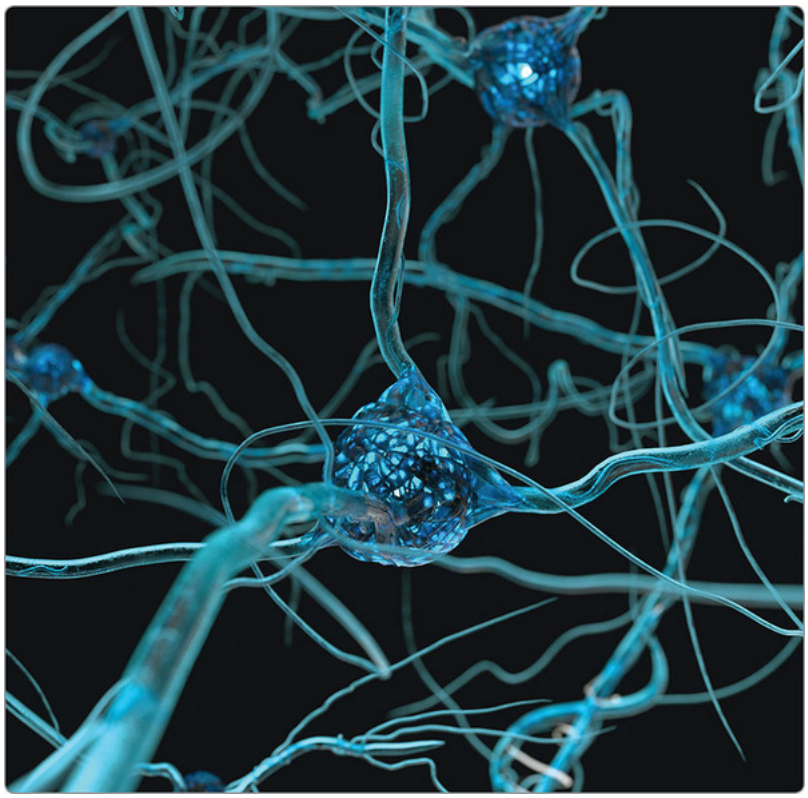
PART I NEURAL FOUNDATIONS OF BEHAVIOR: THE BASIC EQUIPMENT

Chapter 2. Communication Within the Nervous System

Chapter 3. The Organization and Functions of the Nervous System

Chapter 4. The Methods and Ethics of Research

2 COMMUNICATION WITHIN THE NERVOUS SYSTEM



Andriy Onufriyenko / Moment / Getty Images

The Cells That Make Us Who We Are

Neurons

A Further Look | Targeting Ion Channels

Glial Cells

Concept Check

How Neurons Communicate With Each Other

Chemical Transmission at the Synapse

A Further Look | A Neuron Type Found Only in Humans

Regulating Synaptic Activity

Neurotransmitters

A Further Look | Agonists and Antagonists in the Real World

Neural Codes and Neural Networks

A Further Look | Uses and Abuses of Artificial Neural Networks

Concept Check

In Perspective

Chapter Summary

Study Resources

After reading this chapter, you will be able to

2.1 Identify the cells of the nervous system.

2.2 Name the structures of neurons.

2.3 Compare the functions of sensory, motor, and interneurons.

2.4 Understand the roles of different types of glial cell.

2.5 Explain the roles of ions and the cell membrane in nervous system communication.

2.6 Explain how neurotransmitters are involved in communication between neural cells.

2.7 Discuss how neurons work together to generate your experiences of the world.

2.8 Illustrate the ways in which excitation and inhibition are important to the functioning of the nervous system.

Things were looking good for Jim and his wife. She was pregnant with their first child, and they had just purchased and moved into a new home. After the exterminating company treated the house for termites by injecting the pesticide chlordane under the concrete slab, Jim noticed that the carpet was wet and there was a chemical smell in the air. He dried the carpet with towels and thought no more about it, not realizing that chlordane can be absorbed through the skin. A few days later, he developed headaches, fatigue, and numbness. Worse, he had problems with memory, attention, and reasoning. His physician referred him to the toxicology research center of a large university medical school. His intelligence test score was normal, but the deficiencies he was reporting showed up on more specific tests of cognitive ability. Jim and his wife had to move out of their home; at work, he had to accept reduced responsibilities because of his difficulties in concentration and adapting to novel situations. The chlordane had not damaged the structure of his brain as you might suspect, but it had interfered with the functioning of the brain cells by impairing a mechanism called the sodium-potassium pump (Zillmer & Spiers, 2001). Jim's unfortunate case reminds us that the nervous system is as delicate as it is intricate. Only by understanding how it works will we be able to appreciate human behavior, to enhance human performance, and to treat behavioral problems such as drug addiction and psychosis.

THE CELLS THAT MAKE US WHO WE ARE

To understand how the brain works, you must first have at least a basic understanding of the two categories of cells that carry messages back and forth in the brain and throughout the rest of the body. **Neurons** convey sensory information into the brain; carry out the operations involved in thought, feeling, and action; and transmit commands out to the body to control muscles and organs. It is estimated that there are about 86 billion neurons in the human brain (Figure 2.1; Azevedo et al., 2009). This means that there are more neurons in your brain than stars in our galaxy. But as numerous and as important as they are, neurons make up only half of the brain's cells (von Bartheld, Bahney, & Herculano-Houzel, 2016). There are also almost as many glial cells and, as we will see later in the chapter, they are almost as important.

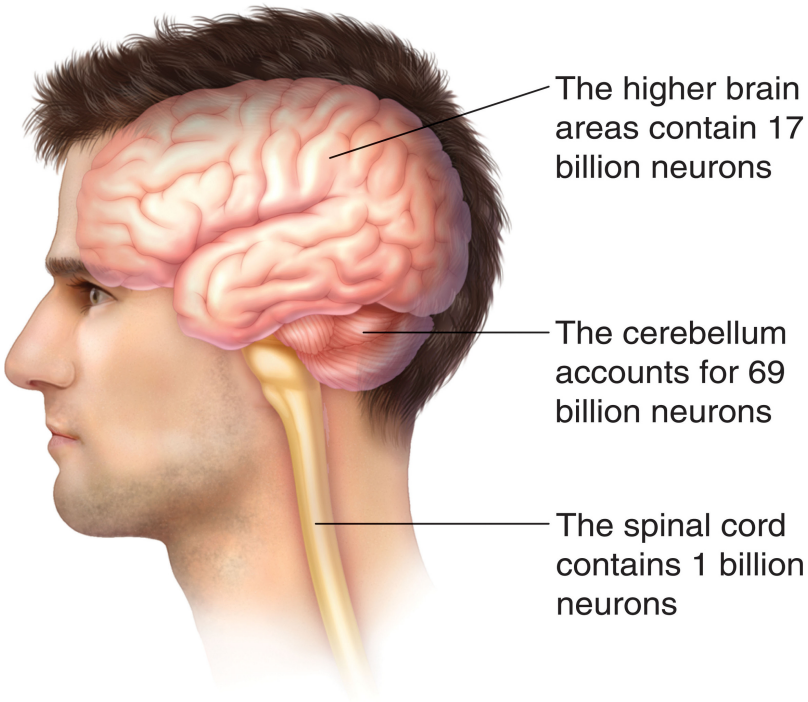


Figure 2.1 Estimated Numbers of Neurons in the Brain and Spinal Cord.

Neurons

Neurons are responsible for all the things we do—our movements, our thoughts, our memories, and our emotions. It is difficult to believe that anything so simple as a cell can measure up to this task, and the burden is on the neuroscientist to demonstrate that this is true. As you will see, the neuron is deceptively simple in its action but impressively complex in its function.

Basic Structure: The Motor Neuron

First, let's look inside a neuron, because we want to show you that the neuron is a cell, very much like other cells in the body. Figure 2.2 is an illustration of the most prominent part of the neuron, the **cell body** or soma. The cell body is filled with a liquid called cytoplasm and contains a number of *organelles*. The largest of these organelles is the *nucleus*, which contains the cell's chromosomes. Other organelles are responsible for converting nutrients into fuel for the cell, constructing proteins and

lipids, and removing waste materials. So far, this could be the description of any cell; now, let's look at the neuron's specializations that enable it to carry out its unique role. Figure 2.3 illustrates a typical neuron. We use "typical" guardedly here, because there are three major kinds of neurons and many variations within those types. The figure illustrates a **motor neuron**, which carries commands to the muscles and organs. It is particularly useful for demonstrating the structure and functions that all neurons have in common.

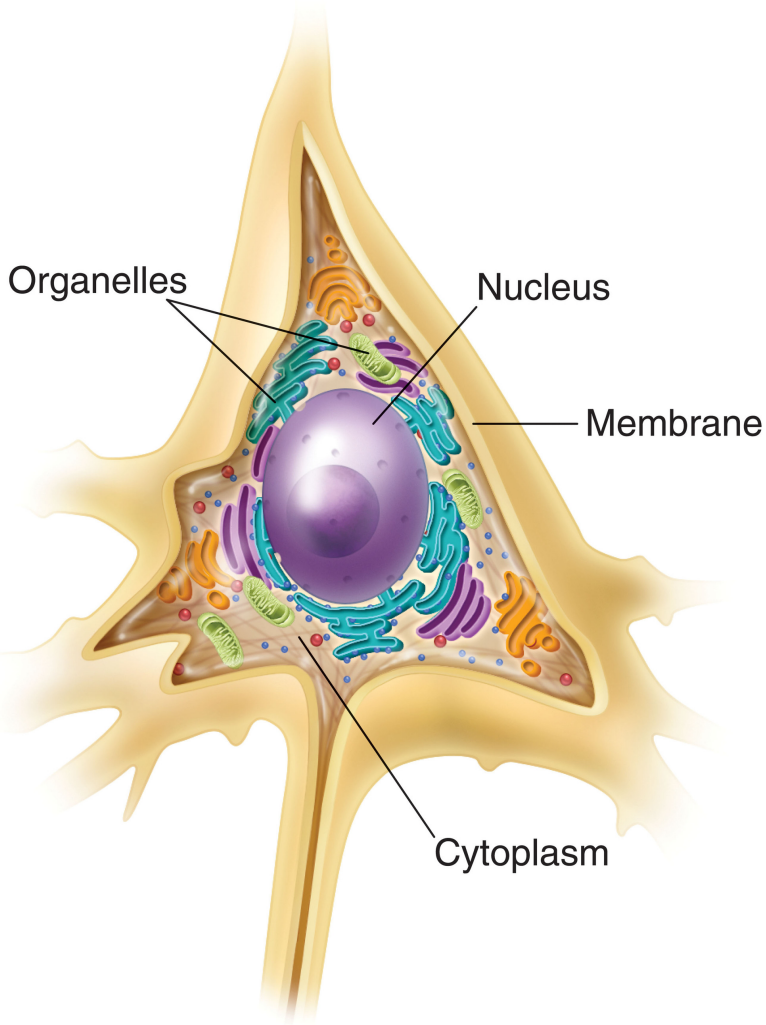
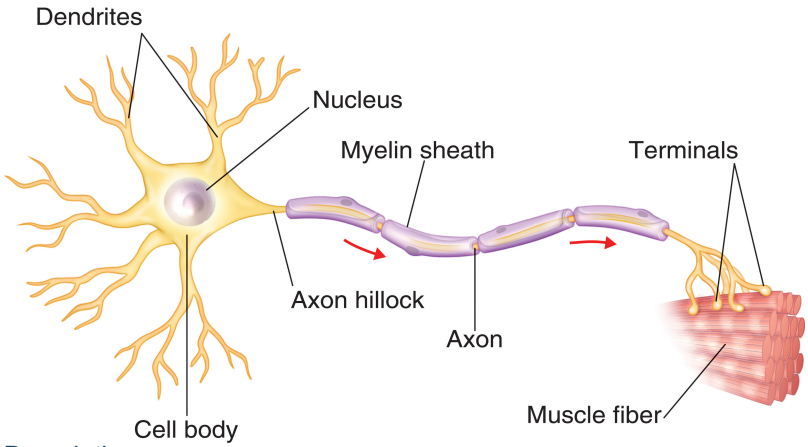


Figure 2.2 Cell Body (Soma) of a Neuron.
Part of the membrane has been removed to show interior features.



Description

Figure 2.3 Components of a Neuron.
The illustration is of a multipolar motor neuron.

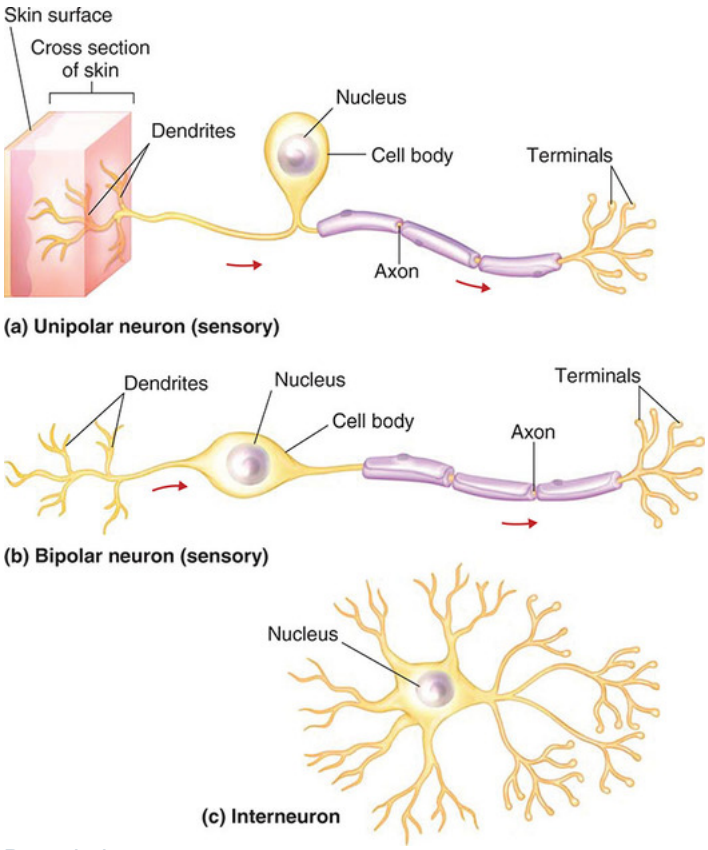
? What are the parts of the neuron?

Dendrites are extensions that branch out from the cell body to receive information from other neurons. Their branching structure allows them to collect information from many neurons. The **axon** extends like a tail from the cell body and carries information to other locations, sometimes across great distances. The myelin sheath that wraps around the axon supports the axon and provides other benefits that we will consider later. Branches at the end of the axon culminate in swellings called **axon terminals**. The terminals contain chemical **neurotransmitters**, which the neuron releases to communicate with a muscle, an organ, or the next neuron in a chain. In our examples, we will talk as if neurons form a simple chain, with one cell sending messages to a single other neuron, and so on; in actuality, a single neuron receives input from many neurons and sends its output to many others.

Neurons are usually so small that they can be seen only with the aid of a microscope. The cell body is the largest part of the neuron, ranging from 0.005 to 0.1 millimeter (mm) in diameter in mammals. (In case you are unfamiliar with metric measurements, a millimeter is about the thickness of a dime.) Even the giant neurons of the squid, favored by researchers for their conveniently large size, have axons that are only 1 mm in diameter. Typical axons are smaller; in mammals, they range from 0.002 to 0.02 mm in diameter. Axons may be as short as 0.1 mm or as long as 30 m in the blue whale (D. H. Smith, 2009).

Other Types of Neurons

The second type of neuron is the sensory neuron. **Sensory neurons** carry information from the body and the outside world into the brain and spinal cord. Motor and sensory neurons have the same components, but they are configured differently. A motor neuron's axon and dendrites extend in several directions from the cell body, which is why it is called a *multipolar* neuron. Sensory neurons can be either *unipolar* or *bipolar*. The sensory neuron in Figure 2.4a is called a unipolar neuron because the single short stalk from the cell body divides into two branches, with dendrites on one side and the axon and terminals on the other. (In the pseudounipolar subtype, both connections to the cell body are axons; that's because its sensory information must travel over a longer distance, from the periphery of the body to the spinal cord and the brain.) Bipolar neurons have an axon on one side of the cell body and a dendritic process on the other (Figure 2.4b). Motor and sensory neurons are specialized for transmission over long distances; their lengths are not shown here in the same scale as the rest of the cell.



Description

Figure 2.4 Sensory Neurons and an Interneuron.
Compare the location of the soma in relation to the dendrites and axon in these neurons and in the motor neuron.

Carolina Hrejsa/Body Scientific Intl.

The third type is neither motor nor sensory. **Interneurons** connect one neuron to another in the same part of the brain or spinal cord. Notice in Figure 2.4c that this neuron is also multipolar, but its axon appears to be missing; for some interneurons, this is so, and when they do have axons, they are often so short that they are indistinguishable from dendrites. Because interneurons make connections over very short distances, they do not need the long axons that characterize their motor and sensory counterparts. In the spinal cord, interneurons bridge sensory neurons and motor neurons to produce a reflex. In the brain, they connect adjacent neurons to carry out the complex processing that the brain is noted for. Considering the major roles they play, it should come as no surprise that interneurons are by far the most numerous neurons.

The different kinds of neurons operate similarly; they differ mostly in their shape, which fits them for their specialized tasks. We will examine how neurons work in the next few sections. The types of neurons and their characteristics are summarized in Table 2.1.

Table 2.1

The Neural Membrane and Its Potentials

The most critical factor in the neuron's ability to communicate is the membrane that encloses the cell. The membrane is exceptionally thin—only about 4 nanometers

TABLE 2.1 The Major Types of Neurons.

TYPE	FUNCTION	FORM AND SOMA LOCATION	DESCRIPTION
Motor	Conducts messages from brain and spinal cord to muscles and organs	Multipolar; central nervous system	Axon, dendrites extend in several directions from cell body
Sensory	Carries information from body and world to brain and spinal cord	Unipolar; peripheral nervous system, cranial nerves	Single short stalk from cell body divides into two branches
		Bipolar; peripheral nervous system	Axon and dendritic processes are on opposite sides of cell body
Interneuron	Conducts information between neurons in same area	Multipolar; central nervous system	Has short or no axon; communicates locally (with nearby neurons)

(billionths of a meter) thick—and is made up of lipid (fat) and protein (van Meer, Voelker, & Feigenson, 2008; Figure 2.5). Each lipid molecule has a "head" end and a "tail" end. The heads of the molecules are water soluble, so they are attracted to the seawater-like fluid around and inside cells. The tails are water insoluble, so they are repelled by the fluid. Therefore, as the heads orient toward the fluid and the tails orient away from the fluid, the molecules turn their tails toward each other and form a double-layer membrane.

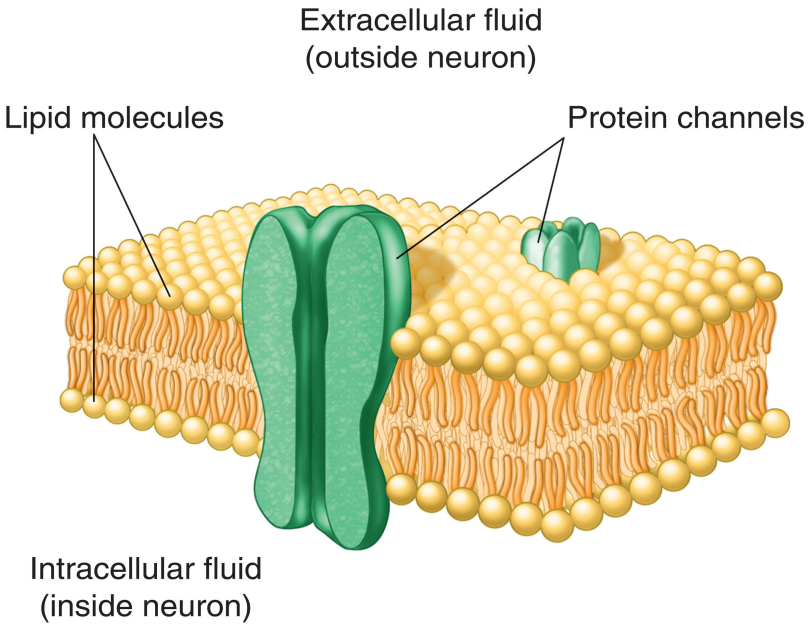


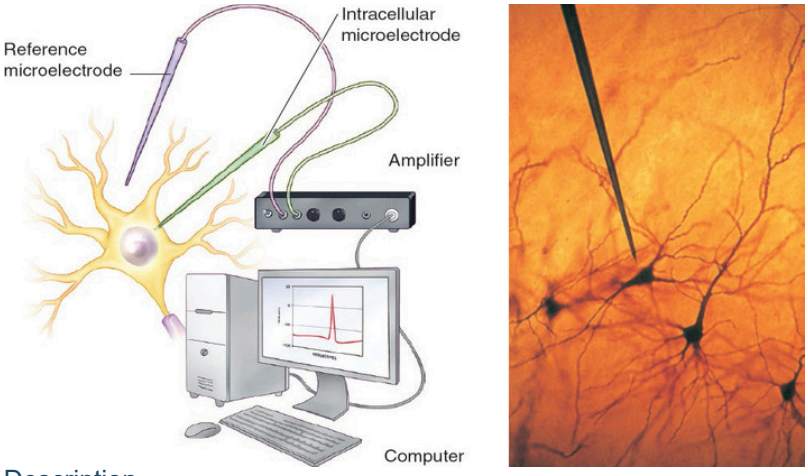
Figure 2.5 Cross Section of the Cell Membrane of a Neuron.
Notice how the lipid molecules form the membrane by orienting their heads toward the extracellular and intracellular fluids.

? What accounts for the resting potential?

The membrane not only holds a cell together but also controls the environment within and around the cell. Some molecules, such as water, oxygen, and most gases, can diffuse through the membrane freely. Many other substances are barred from crossing the membrane. Still others are allowed limited passage through protein channels (shown in the figure in green) that open and close under specific circumstances. This selective permeability contributes to the most fundamental characteristic of neurons, **polarization**, which means that there is a difference in electrical charge between the inside and outside of the neuron. A difference in electrical charge between two points, such as the poles of a battery or between the inside and outside of a neuron, is also called a **voltage**.

The Resting Potential. Just as you can measure the voltage of a battery, you can measure a neuron's voltage (Figure 2.6). By arbitrary convention, the voltage is expressed as a comparison of the inside of the neuron with the outside. The difference in charge between the inside and outside of the membrane of a neuron at rest is called the **resting potential**. This voltage is negative and varies anywhere

from –40 to –80 millivolts (mV) in different neurons but is typically around –70 mV. You should understand that neither the inside of the neuron nor the outside has a voltage, because a voltage is a *difference* and is meaningful only in comparison with another location. Note that this voltage is quite small—the voltage of a standard 1.5-V battery is 25 times greater. No matter; we're moving information, and very little power is required.

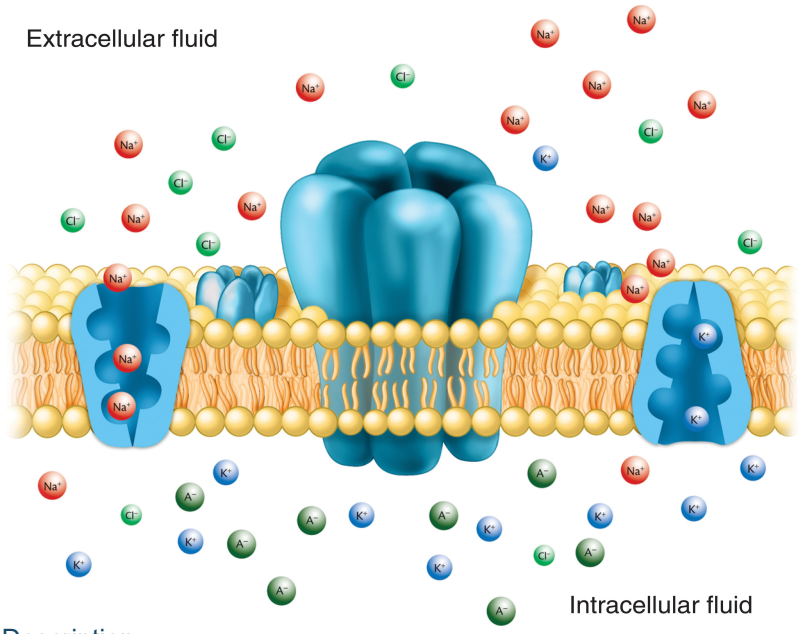


Description

Figure 2.6 Recording Potentials in a Neuron.
Potentials are being recorded in the axon of a neuron, with an electrode inside the cell and one in the fluid outside. Due to the size of neurons, the electrodes have microscopically small tips. On the right, a highly magnified view shows the size of a microelectrode relative to that of neurons. Electrodes for recording inside neurons are even smaller.

Right Photo: Bob Jacobs, Colorado College

The resting potential is due to the unequal distribution of electrical charges on the two sides of the membrane. The charges come from **ions**, atoms that have lost or gained one or more electrons. Sodium ions (Na^+) and potassium ions (K^+) are positively charged. Chloride ions (Cl^-) are negative, as are certain proteins and amino acids that make up the organic anions (A^-). The fluid outside the neuron contains mostly Na^+ and Cl^- ions, and the ions inside the neuron are mostly K^+ and A^- (Figure 2.7). The inside of the neuron has more negative ions than positive ions, whereas the ions on the outside are mostly positive, and this makes the resting potential negative.



Description

Figure 2.7 Distribution of Ions Inside and Outside the Resting Neuron.
Ions on the outside are mostly Na^+ (red) and CL^- (green) ions; inside, the ions are mostly K^+ ions (blue) and organic anions (dark green). In the middle of the membrane is an ion channel, which is closed and not allowing ions through; on the left, a sodium-potassium pump is discharging three Na^+ ions outside the neuron, while on the right, an identical pump is returning two K^+ ions to the inside.

If you remember from grade-school science that molecules tend to diffuse from an area of high concentration to one of low concentration, then you are probably wondering how this imbalance in ion distribution can continue to exist. In fact, two forces do work to balance the location of the ions. Because of the **force of diffusion**, ions tend to move through the membrane to the side where they are less concentrated. And as a result of **electrostatic pressure**, ions are repelled from the side that is similarly charged and attracted to the side that is oppositely charged.

In spite of these two forces, a variety of other influences keep the membrane polarized. Both forces would move the organic anions out, but they are too large to pass through the membrane. Their negative charge then repels the chloride ions, so the force of diffusion is unable to move those ions inside. As a result, the “real player” then becomes the potassium ions. Potassium’s force of diffusion is stronger than its electrostatic pressure, and although the potassium and sodium channels are both closed during resting, potassium can slip through the membrane itself more readily than the other ions.

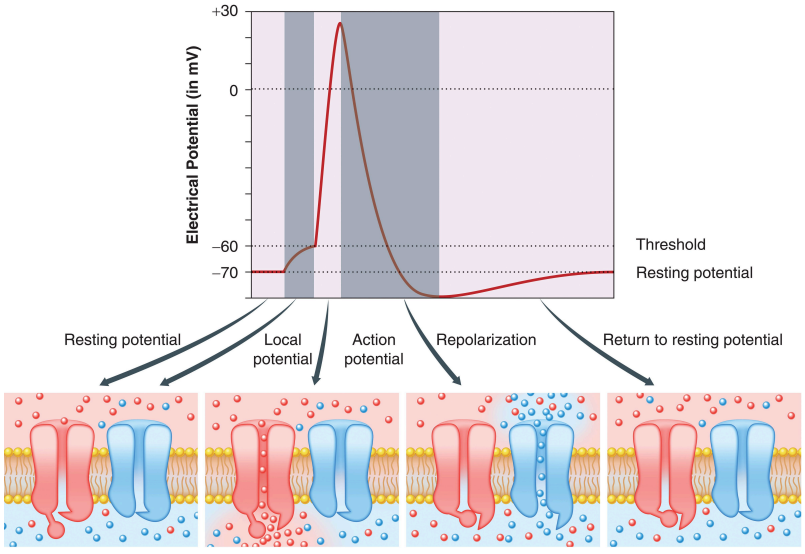
Another significant contributor to polarity is the **sodium-potassium pump**, which consists of large protein molecules that move sodium ions through the cell membrane to the outside and potassium ions back inside. It moves three sodium ions out for every two potassium ions it moves inside, which helps keep the inside of the membrane more negative than the outside. The pump’s operation is a metabolic process, which means that it uses energy; in fact, it accounts for an estimated 40% of the neuron’s energy expenditure. But you will soon see that this energy is well spent, because the resting potential stores the energy to power the action potential, the major signal in the nervous system.

Ion Channels and Local Potentials. Before we move on, we need a better understanding of how the ion channels work. These are pores in the membrane formed by proteins, and they gate the flow of ions between the extracellular and intracellular fluids. Chemically gated channels can be opened by ligands

(neurotransmitters or hormones), and electrically gated channels are opened by a change in the electrical potential of the membrane.

A neuron is usually stimulated by inputs that arrive on the neuron's dendrites and/or cell body from another neuron or from a sensory receptor. The effect may be excitatory or inhibitory, depending on the ligand and the characteristics of the receptors. An excitatory signal causes a slight partial depolarization, which means that the polarity in a small area of the membrane is shifted toward zero. This partial depolarization disturbs the ion balance in the adjacent membrane, so the disturbance flows down the dendrites and across the cell membrane. This looks at first like the way the neuron might communicate its messages through the nervous system; however, because a partial depolarization is decremental—it dies out over distance—it is effective over only very short distances. For this reason, the partial depolarization is often called the *local potential*. The ion channels in the axon are electrically gated, and they have unique physical properties. If the local potential exceeds the threshold for activating those channels, typically about 10 mV more positive than the resting potential, it will initiate an action potential.

Action Potentials. The **action potential** is an abrupt depolarization of the membrane that allows the neuron to communicate over long distances. The voltage across the resting neuron membrane is stored energy, just as the term resting *potential* implies. Imagine countless sodium ions being held outside the neuron against the combined forces of diffusion and electrostatic pressure (Figure 2.8a). A stimulus that partially depolarizes a segment of membrane causes voltage-gated sodium ion channels to open; this allows nearby sodium ions to rush into the axon at a rate 500 times greater than normal (Figure 2.8b). They are propelled into the cell's interior so rapidly that the movement is often described as explosive. A small area inside the membrane becomes fully depolarized to zero; the potential even overshoots to around +30 or +40 mV, making the interior at that location temporarily positive.



Description

Figure 2.8 Ion Movement and Voltages During the Neural Impulse.

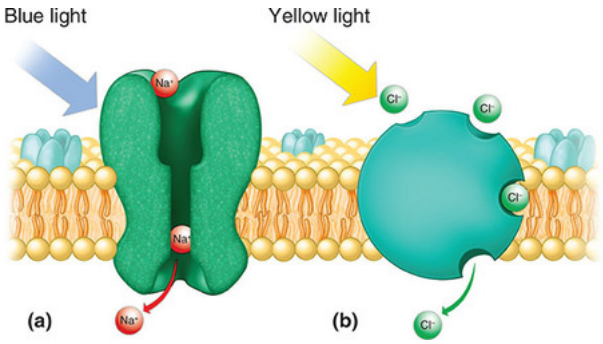
Just as abruptly as the neuron "fires," it begins to recover its resting potential. At the peak of the action potential, voltage sensors in the sodium channels detect the

depolarization and close a gate, inactivating the channel and preventing further sodium ion influx (Catterall, 2010). The depolarization also causes voltage-gated potassium ion channels to open; the positive charge and the higher concentration of potassium ions inside the membrane combine to force potassium ions out. This outward flow of positive potassium ions lowers the axon voltage to its resting potential and sometimes a bit beyond (Figure 2.8c). In total, the action potential lasts about 1 millisecond (one thousandth of a second); the actual duration varies among individual neurons. (Obviously, these channels are what make the neuron operate; A Further Look (page 28) describes how they are exploited by nature and in research and medicine.)

A Further Look:

Targeting Ion Channels

Stories of Brain & Behavior



Modified Membrane Enables Light Control of Neuron Activity.
(a) Blue light activates a channel from green algae; the channel allows positive ions to flow inward, triggering neural impulses. (b) Yellow light activates a chloride pump from bacteria; chloride ions hyperpolarize the neuron.

Source: Adapted from "Controlling Neural Circuits With Light," by M. Häusser and S. L. Smith, 2007, *Nature*, 446, 617–619 (Figure 1a, p. 617).

The Japanese delicacy fugu, or puffer fish, produces an exciting tingling sensation in the diner's mouth; improperly prepared, it causes numbness and weakness and, in some cases, a paralysis of the respiratory muscles that has claimed the lives of hundreds of culinary risk takers. The fish's natural poison, tetrodotoxin (TTX), blocks sodium channels and prevents neurons from firing (Siegelbaum & Kandel, 2013). Researchers are examining TTX as a potential replacement for opiate painkillers (Gorey, 2019; Nieto et al., 2012), so this dangerous toxin might lead to new treatments for chronic pain. Other **neurotoxins** (neuron poisons) are found in snake venoms, which block sodium, potassium (Benoit & Dubois, 1986; Fertuck & Salpeter, 1974), or calcium channels, and scorpion venom, which keeps sodium channels open, prolonging the action potential (Catterall, 1984; Chuang, Jaffe, Cribbs, Perez-Reyes, & Swartz, 1998; Pappone & Cahalan, 1987).

Interfering with neuron functioning can be useful, though; for example, most local anesthetics prevent neuron firing by blocking sodium channels (Ragsdale, McPhee, Scheuer, & Catterall, 1994), and some general anesthetics hyperpolarize the neuron by opening potassium channels and allowing the potassium ions to leak out (Nicoll &

Madison, 1982; A. J. Patel et al., 1999). The cone snail of the South Seas can penetrate a wet suit with its proboscis and inject toxins that will kill a human in half an hour, but the various species' thousands of toxins that target sodium, potassium, or calcium channels or block neurotransmitter receptors are in demand by researchers developing pain relievers and drugs for preventing heart attacks and epilepsy (L. Nelson, 2004; Oliviera & Teichert, 2007).

An exciting new research strategy known as **optogenetics** allows researchers to create light-responsive channels (as well as receptors) in neurons so that they can be controlled by light. Different types of channels are triggered by different wavelengths of light, which allows the researcher either to accelerate or to inhibit firing. The procedure is being used to understand the circuitry in a variety of behaviors and brain processes and is showing potential for use in therapeutic procedures.

Only a relatively few ions very near the two sides of the membrane have participated in the action potential; these dislocated ions quickly diffuse into the surrounding fluid, and the membrane potential returns to its resting level (Figure 2.8d). Eventually, though, the ions must be returned to their original locations, or the neuron cannot continue firing; the sodium-potassium pump takes care of this. (Perhaps you can see now why Jim was in such a bad way after his bout with chlordane.)

? What is the role of the sodium-potassium pump following an action potential?

The depolarization that occurs during the action potential triggers nearby sodium channels to open as well. Thus, a new action potential is triggered right next to the first one. That action potential in turn triggers another farther along, creating a chain reaction of action potentials that move through the axon; thus, a signal flows from one end of the neuron to the other. Nothing physically moves down the axon. Instead, a series of events occurs in succession along the axon's length, much as a line of dominoes standing on end knock each other over when you tip the first one. When the action potential reaches the terminals, they pass the signal on to the next neuron in the chain (or to an organ or a muscle). The transmission of signals from neuron to neuron is covered later; for now, the action potential needs to be examined a bit further.

The action potential differs in two important ways from the local potential that initiates it. First, the local potential is a **graded potential**, which means that it varies in magnitude with the strength of the stimulus that produced it. The action potential, by contrast, is *ungraded*; it operates according to the *all-or-none law*, which means that it occurs at full strength or it does not occur at all. A larger graded potential does not produce a larger action potential; like the fuse of a firecracker, the action potential depends on the energy stored in the neuron, in this case, due to the difference in ion concentrations between the two sides of the membrane. A second difference is that the action potential is **nondecremental**; it travels down the axon without any decrease in size, propagated anew and at full strength at each successive point along the way. The action potential thus makes it possible for the neuron to conduct information over long distances.

? How is an action potential different from a graded potential?

However, because the action potential is all-or-none, its size cannot carry information about the intensity of the initiating stimulus. One way stimulus intensity is represented is in the number of neurons firing. The voltage sensitivity of sodium channels varies among neurons, resulting in different thresholds; a more intense stimulus will recruit firing in neurons with higher thresholds and, therefore, in more neurons. There is, though, a way in which the individual neuron can encode stimulus strength, as you will see in the discussion of refractory periods.

? What are the absolute and relative refractory periods?

Refractory Periods

If you remember a few paragraphs back, we stated that the flow of an action potential down the axon was like knocking down a line of dominoes. And just as you must go through and reset the dominoes so that they can fall again, the ion channels must be reset before the neuron can fire again. During the action potential and initial recovery, the sodium ion channels are open and unresponsive to further stimulation, no matter how intense; this time is referred to as the **absolute refractory period**. This delay in responsiveness has two important effects. First, the 1- to 2-millisecond duration of the absolute refractory period limits how fast the neuron can generate new action potentials; a study of cortical *fast-spiking neurons* found maximal rates of 453 per second in humans, 611 in monkeys, and 342 in mice (B. Wang et al., 2016). Second, because the ion channels behind the action potential are still recovering, the impulse can propagate only down the axon toward the dendrites, not back toward the cell body. This makes neural transmission unidirectional, which has the secondary effect of preventing the neuron from "locking up." If recovery were immediate, activity would self-propagate in both directions from an ongoing action potential; this would result in impulses moving repeatedly back and forth along the axon, which would block the ability to respond to newly arriving messages.

At the end of the absolute refractory period, the sodium channels have closed, so the neuron is able to fire again. But the potassium channels remain open for an additional 3 or 4 milliseconds, and as potassium ions continue to exit the neuron, the polarity is driven slightly more negative than the resting potential (the "dip" in Figure 2.8). During the resulting **relative refractory period**, another action potential can be generated but only by a stronger-than-threshold stimulus. A stimulus that is slightly greater than this temporarily higher threshold will cause the neuron to fire again before the end of the relative refractory period; with progressively stronger stimuli, the neuron will fire increasingly earlier and, therefore, at a higher rate. Thus, the axon encodes stimulus intensity not in the size of its action potential but in its firing rate, an effect called the **rate law**.

Glial Cells

Glial cells are nonneural cells that provide a number of supporting functions to neurons. The name *glia* is derived from the Greek word for "glue," which gives you some idea of how the role of glial cells has been viewed in the past. However, glial cells do much more than hold neurons together. One of their most important functions is to increase the speed of conduction in neurons.

Myelination and Conduction Speed

Survival depends in part on how rapidly messages can move through the nervous system, enabling the organism to pounce on its prey, outrun a predator, or process language quickly. The speed with which the fastest neurons conduct their impulses approaches 120 meters (m) per second (s), or about 270 miles per hour (435 km/hr). This seems fast, but the speed of electricity flowing through a wire, the analogy sometimes used to describe neural conduction, is up to 690 times faster. Because conduction speed is so critical to survival, strategies have evolved for increasing it. One way is to develop larger-diameter axons, which provide less resistance to the flow of electrical potentials. By evolving motor neurons with 0.5-mm-thick axons, the squid has achieved conduction speeds of 30 m/s, compared with 1 m/s in the smallest neurons.

However, conduction speed increases not in direct proportion to axon size but closer to the square of the diameter (W. A. H. Rushton, 1951). To reach our four-times-greater maximum conduction speed of 120 m/s, our axons would have to be $4^2 = 16$ times larger than the squid axon, or 8 mm in diameter (the size of a large pea)! Obviously, your brain would be larger than you could carry around. In other words, if axon size were the only way to achieve fast conduction speed, *you* would not exist. Vertebrates (animals with backbones) have developed another solution, myelination. Two types of glial cells produce **myelin**, a fatty tissue that wraps around the axon (like a jellyroll) to insulate it from the surrounding fluid and from other neurons. Only

the axon is covered, not the cell body. Myelin is produced in the brain and spinal cord by glial cells called **oligodendrocytes** and in the rest of the nervous system by **Schwann cells** (Figure 2.9). Almost 75% of the glial cells in the brain are myelin-producing oligodendrocytes (Pillay & Manger, 2007).

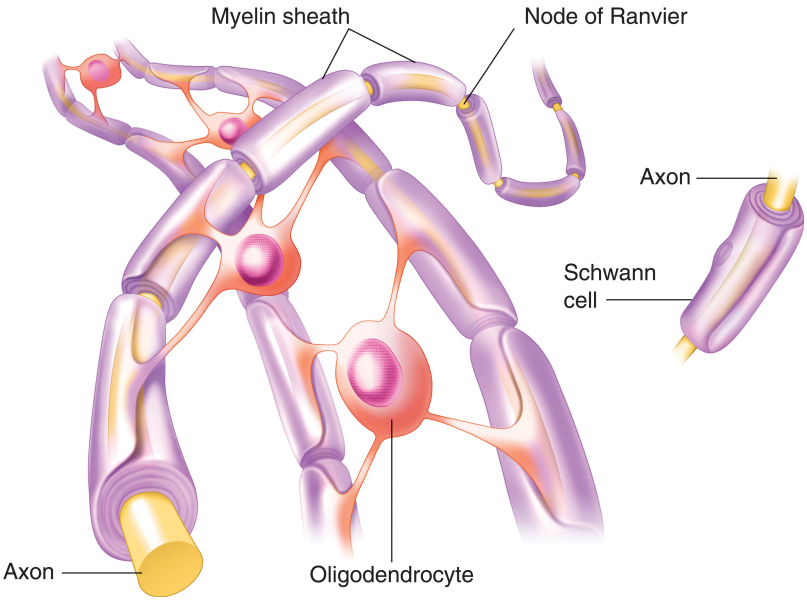


Figure 2.9 Oligodendrocytes Produce Myelin for Axons.
A single oligodendrocyte provides myelin for multiple segments of the axon and for multiple neurons. A Schwann cell covers only one segment of an axon.

? What are the functions of glial cells?

Because there are very few sodium channels under the myelin sheath, action potentials cannot occur there; conduction under myelinated areas is by local graded potential (Waxman & Ritchie, 1985). However, myelin appears in segments about 1 mm long, with a gap of one or two thousandths of a millimeter between segments; these gaps in the myelin sheath are called **nodes of Ranvier** (see Figure 2.9). At each node of Ranvier, where the membrane is exposed and there are plenty of sodium channels, the graded potential triggers an action potential. Action potentials thus appear to jump from node to node in a form of transmission called **saltatory conduction**.

This arrangement has three benefits. First, the insulating effect of myelin reduces an electrical effect of the membrane called capacitance. Because capacitance slows the movement of ions down the axon, the graded potential gets a big boost in speed. The overall effect of myelination is the equivalent of increasing the axon diameter 100 times (Koester & Siegelbaum, 2013). Second, the breaks in the myelination mean that the signal is regenerated by an action potential at every node of Ranvier. Third, myelinated neurons use much less energy because there is less work for the sodium-potassium pump to do.

Some diseases, such as multiple sclerosis, destroy myelin. As myelin is lost, the capacitance rises, reducing the distance that graded potentials can travel before dying out. The individual is worse off than if the neurons had never been myelinated; because there are few voltage-sensitive sodium channels under the myelin sheath (Ritchie & Rogart, 1977), action potentials may not be generated in the previously myelinated area. Therefore, conduction slows or stops in affected neurons.

Other Glial Functions

There are several types of glial cells, and they make numerous contributions to neural functioning. During fetal development, *radial glia* form scaffolds that guide new neurons to their destinations. Later on, *microglia* provide energy to neurons and respond to injury and disease by removing cellular debris. Neurons form seven times as many connections in the presence of the type of glia called *astrocytes*, and they start to lose their synapses if astrocytes are removed from the culture dish (Pfrieger & Barres, 1997; Ullian, Sapperstein, Christopherson, & Barres, 2001; see Figure 2.10). Astrocytes also appear to play a key role in learning, as Figure 2.11 demonstrates (X. Han et al., 2013; Suzuki et al., 2011). Later in this chapter, you will see that glial cells play a direct role in neural activity.

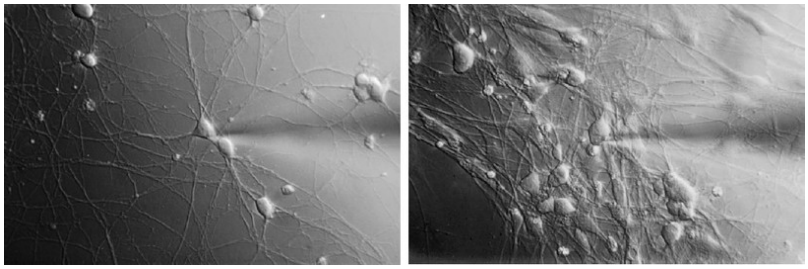
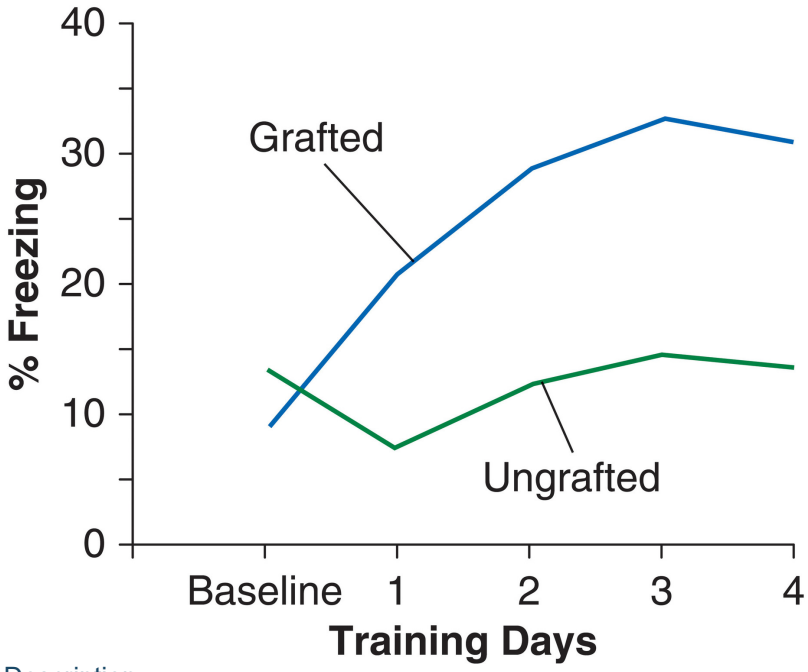


Figure 2.10 Glial Cells Increase the Number of Connections Between Neurons. Neurons were cultured for 5 days in (a) the absence of glial cells and (b) the presence of glia. The number of neurons was similar in both cultures; the greater density on the right is due to increased connections among both neurons.

Source: From F. W. Pfrieger and B. A. Barres, "Synaptic Efficacy Enhanced by Glial Cells In Vitro," *Science*, Vol. 277, p. 1684, 1997. Reprinted with permission from AAAS.



Description

Figure 2.11 Human Glial Cells Enhance Conditioning in Mice.
Mice receiving brain grafts of human glial cells rapidly learned a fear response ("freezing" to a tone that signaled an upcoming electric shock), while ungrafted controls showed little or no improvement.

Source: Adapted from Figure 6B of "Forebrain Engraftment by Human Glial Progenitor Cells Enhances Synaptic Plasticity and Learning in Adult Mice," by Xiaoning Han et al., 2013, *Cell Stem Cell*, 12, p.

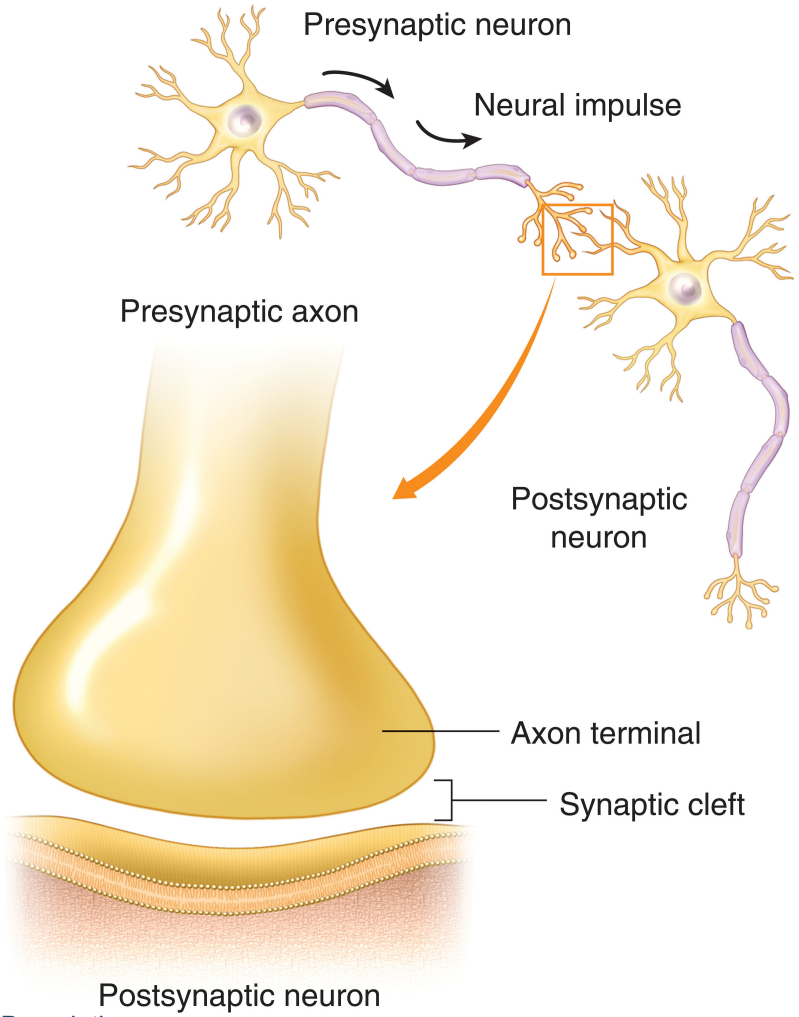
Concept Check

Take a Minute to Check Your Knowledge and Understanding

- How is information conducted in the axon?
- How does the all-or-none law limit information transmission?
- What benefits do the refractory periods provide?
- How does myelin speed up conduction in axons?

HOW NEURONS COMMUNICATE WITH EACH OTHER

Before the late 1800s, microscopic examination suggested that the brain consisted of a continuous web called a reticulum. At that point, however, Camillo Golgi developed a new tissue-staining method that helped anatomists see individual neurons by randomly staining some entire cells without staining others (see the discussion of staining methods in Chapter 4). With this technique, the Spanish anatomist Santiago Ramón y Cajal (1937/1989) was able to see that each neuron is a separate cell. (See the For Further Reading section at the end of this chapter for more information about Ramón y Cajal's seminal work on describing the nervous system.) The connection between two neurons is called a **synapse**, a term derived from the Latin word that means "to grasp." The neurons are not in direct physical contact at the synapse but are separated by a small gap called the **synaptic cleft**. Two terms will be useful to us in the following discussion: The neuron that is transmitting to another is called the **presynaptic** neuron; the receiving neuron is the **postsynaptic** neuron (Figure 2.12).



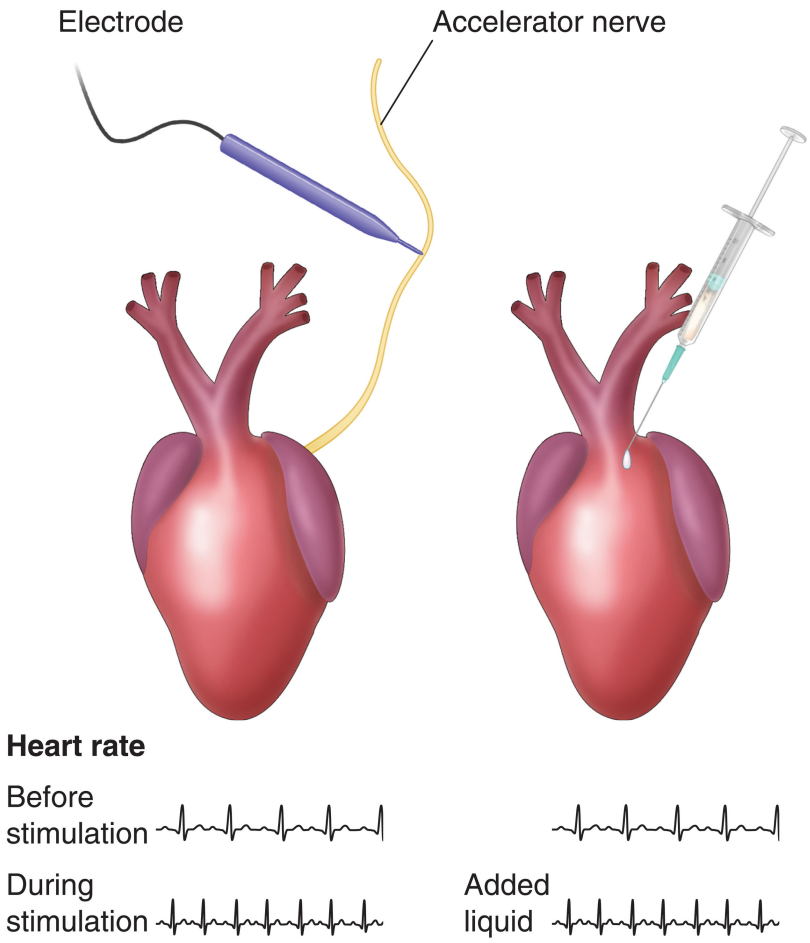
Description

Figure 2.12 The Synapse Between a Presynaptic Neuron and a Postsynaptic Neuron.
Notice the separation between the presynaptic axon terminal and the postsynaptic neuron.

Chemical Transmission at the Synapse

Until the 1920s, physiologists weren't sure whether neurons communicated at the synapse by an electrical current or by releasing a chemical. The German physiologist Otto Loewi believed that synaptic transmission was chemical, but he did not know how to test his hypothesis. One night, Loewi awoke from sleep with the solution to his problem (Loewi, 1953). He wrote his idea down so that he would not forget it, but the next morning, he could not read his own writing. He recalled that day as the most "desperate of my whole scientific life" (p. 33). But the following night, he awoke again with the same idea; taking no chances, he rushed to his laboratory. There he dissected out the beating hearts of two frogs and bathed them in a salt solution. He applied electrical stimulation to the vagus nerve attached to one of the hearts, which slowed the heartbeat. Then he extracted some of the salt solution, which he assumed would have captured any chemical that might have been released. When he applied this salt solution to the second heart, that heart slowed, too, just as Loewi predicted. Then he stimulated the accelerator nerve of the first heart, which caused the heart to beat faster. When he transferred the solution from the first heart to the second, this time it sped up (Figure 2.13). So Loewi demonstrated for the first time that

transmission at the synapse is chemical and that neurons release at least two different chemicals with opposite effects.



Description

Figure 2.13 Loewi's Experiment Demonstrating Chemical Transmission in Neurons. Loewi stimulated the first frog heart. When he transferred fluid from it to the second heart, it produced the same effect there as the stimulation did in the first heart.

It turned out later that some neurons do communicate electrically by passing ions through channels that connect one neuron to the next; their main function appears to be synchronizing activity in nearby neurons (M. V. L. Bennett & Zukin, 2004). In addition, some neurons release a gas transmitter. Still, Loewi was essentially correct because the majority of synapses are chemical. (By the way, if this example suggests to you that the best way to solve a problem is to "sleep on it," keep in mind that such insight occurs only when people have paid their dues in hard work beforehand!)

At chemical synapses, neurotransmitters are stored in the terminals in membrane-enclosed bubbles called **vesicles**; the term means, appropriately, "little bladders." When the action potential arrives at the terminals, it opens channels that allow calcium ions to enter the terminals from the extracellular fluid. The calcium ions cause the vesicles clustered nearest the membrane to fuse with the membrane. The membrane opens there, and the transmitter spills out and diffuses into the cleft in a process called *exocytosis* (Figure 2.14).

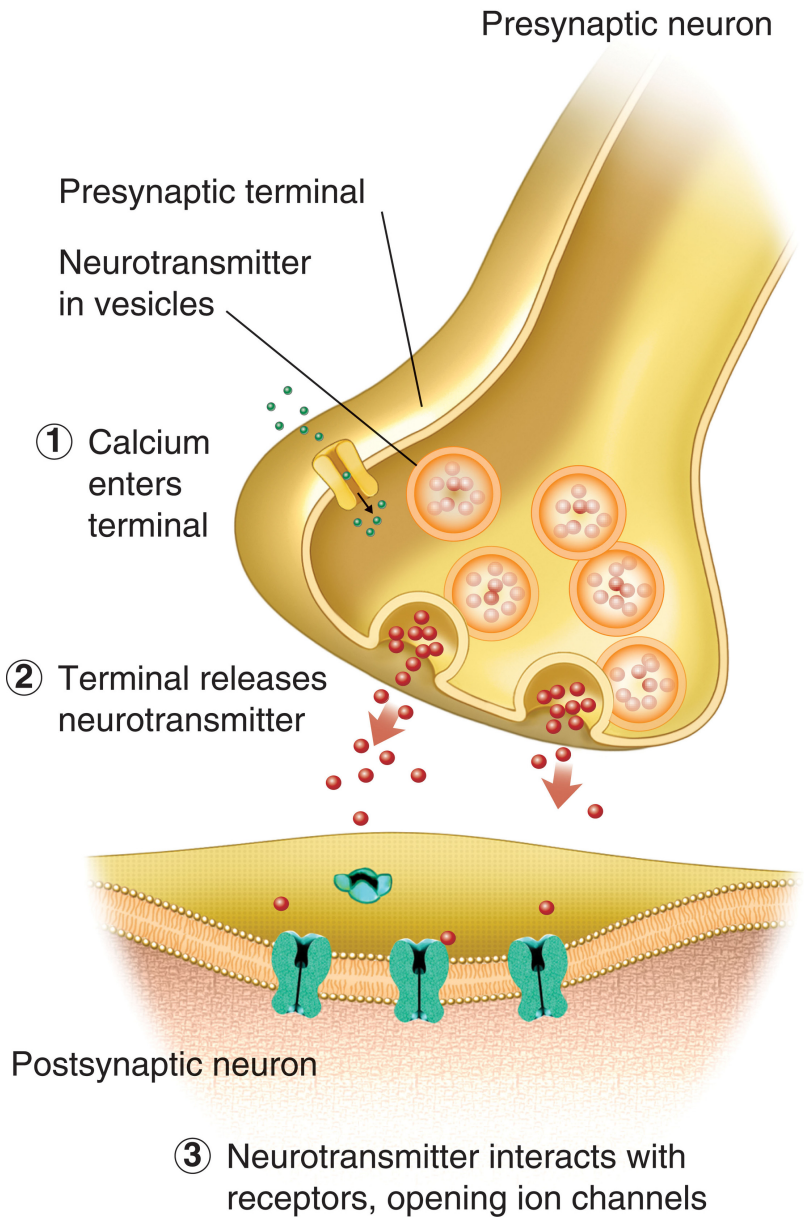


Figure 2.14 A Presynaptic Terminal Releases the Neurotransmitter at the Synapse.

? How does synaptic transmission differ from transmission in the axon?

On the postsynaptic neuron, the neurotransmitter docks with specialized protein receptors that match the molecular shape of the transmitter molecules like a key in a lock (see Figure 2.14). Activation of these receptors opens the ion channels, allowing ions to flow across the membrane. **Ionotropic receptors** form the ion channel and open quickly to produce the immediate reactions required for muscle activity and sensory processing. **Metabotropic receptors** open channels indirectly through a second messenger; they act slowly and produce longer-lasting effects. Opening the channels is what sets off the graded potential that initiates the action potential. You will see in the next section that the effect this has on the postsynaptic neuron depends on which receptors are activated.

The chemical jump across the synapse takes a couple of milliseconds; that is a significant slowing compared with transmission down the axon. In a system that

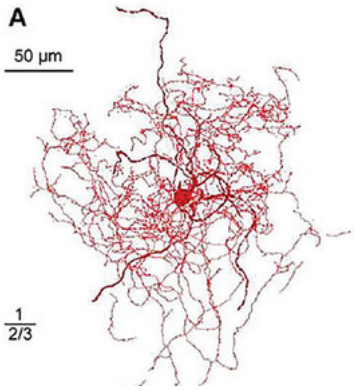
places a premium on speed, inserting gaps in the neural pathway that slow down transmission must have some compensating benefit. As you will see in the following sections, synapses add important complexity to the simple all-or-none response in the axon.

Excitation and Inhibition

Opening ion channels on the dendrites and cell body has one of two effects: It can cause the local membrane potential to shift in a positive direction toward zero, partially depolarizing the membrane, or it can shift the potential farther in the negative direction. **Partial depolarization** is excitatory and facilitates the occurrence of an action potential; increased polarization, or **hyperpolarization**, is inhibitory and makes an action potential less likely to occur. The value of excitation is obvious, but inhibition can communicate just as much information as excitation does. Also, the message becomes more complex because input from one source can partially or completely negate input from another. In addition, inhibition helps prevent runaway excitation; one cause of the uncontrolled neural storms that sweep across the brain during an epileptic seizure is a deficiency in receptors for the inhibitory transmitter GABA (Baulac et al., 2001). Lithium, which is used to reduce manic symptoms of bipolar disorder, decreases excitatory neurotransmitters while increasing GABA transmission (Malhi, Tanious, Das, Coulston, & Berk, 2013). A Further Look describes an intriguing new finding about the importance of inhibition.

A Further Look:

A Neuron Type Found Only in Humans



A rosehip neuron in Layer 1 of the human cortex.

Source: Boldog, E., Bakken, T. E., Hodge, R. D., Novotny, M., Aevermann, B. D. et al. (2018). Transcriptomic and morphophysiological evidence for a specialized human cortical GABAergic cell type. Nature Neuroscience, 21, 1185–1195. Reprinted with permission.

In 2018, two teams of researchers collaborated to publish a description of a new neuron type that so far has been found only in humans (Boldog et al., 2018). It is a very small, compact neuron, with a bushy set of dendrites; the term *rosehip* was chosen because its appearance resembles a rose after it has lost its petals. Found in the outermost layer of the cortex (Layer 1), the neurons connect with a type of neuron in Layer 3 called pyramidal cells because of the conical shape of their cell body. When human pyramidal neurons fire, they also send excitatory output from their dendrites. The rosehip neurons appear to be exclusively inhibitory, and they produce dense synaptic connections on the pyramidal cell dendrites; the researchers suggest that the rosehip neurons' role may be to regulate this dendritic excitation.

When the research teams looked for rosehip neurons in rodents, they could not find them, which may make them one of the very few uniquely human aspects of the nervous system. Interestingly, pyramidal cells in mice lack the excitatory "backpropagation" that characterizes human pyramidal cells, which may explain why humans have rosehip neurons and mice apparently do not. The researchers also found patterns of gene expression in the rosehip neurons that have been implicated in neuropsychiatric disease, so one of their next steps is to see if the neurons are involved in these disorders (Servick, 2018).

What determines whether the effect on the postsynaptic neuron is exciting or inhibiting? It depends on a combination of which transmitter is released and the type of receptors on the postsynaptic neuron. A particular transmitter can have an excitatory effect at one location in the nervous system and an inhibitory effect at another; however, some transmitters typically produce excitation, and others most often produce inhibition. If the receptors open sodium channels, this produces a partial depolarization of the dendrites and cell body, which acts as an **excitatory postsynaptic potential (EPSP)**. Other receptors open potassium channels, chloride channels, or both; as potassium moves out of the cell or chloride moves in, it produces a hyperpolarization of the dendrites and cell body, or an **inhibitory postsynaptic potential (IPSP)**.

At this point, there is only a graded local potential. This potential spreads down the dendrites and across the cell body to the *axon hillock* (where the axon joins the cell body). Here, a positive graded potential that surpasses threshold will produce an action potential; a negative graded potential will make it less likely to be generated. Most neurons have a baseline rate of spontaneous action potential generation; EPSPs will increase this rate, while IPSPs will decrease the rate of firing (Figure 2.15). So now another form of complexity has been added at the synapse: The message to the postsynaptic neuron can *modulate* the rate of firing, not just turn it on or off.

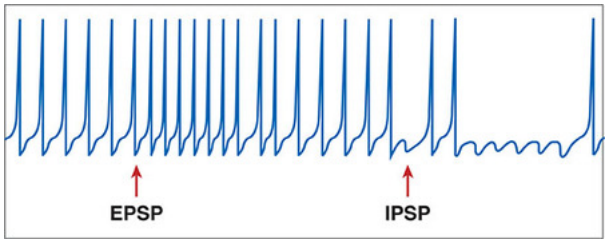


Figure 2.15 Effect of Excitation and Inhibition on Spontaneous Firing Rate.

Source: Adapted from *Principles of Neural Science*, 5th ed., by E. R. Kandel et al., p. 213. © 2013, McGraw-Hill Companies, Inc.

You should not assume that excitation of neurons always corresponds to activation of behavior or that inhibition necessarily suppresses behavior. An EPSP may activate a neuron that has an inhibitory effect on other neurons, and an IPSP may reduce activity in a neuron that has an inhibitory effect on other neurons, increasing their activity. An example of this paradox at the behavioral level is the effect of Ritalin. Ritalin and many other medications used to treat attention-deficit/hyperactivity disorder (ADHD) in children are in a class of drugs called stimulants, which increase activity in the nervous system. Yet in low doses, they calm hyperactive individuals and improve their ability to concentrate and focus attention (D. J. Cox, Merkel, Kovatchev, & Seward, 2000; Mattay et al., 1996). They do this by increasing stimulating neurotransmitters in frontal areas of the brain that normally restrain behavior, where activity has been found to be abnormally low in people with ADHD (Berridge et al., 2006; Faigel, Szuajderman, Tishby, Turel, & Pinus, 1995).

Next, you will see that the ability to combine the inputs of large numbers of neurons expands the synapse's contribution to complexity even further.

What are summation and integration?

Postsynaptic Integration

The output of a single neuron is not enough by itself to cause a postsynaptic neuron to fire or to prevent it from firing. In fact, an excitatory neuron may depolarize the membrane of the postsynaptic neuron by as little as 0.2 to 0.4 mV (Siegelbaum, Kandel, and Yuste, 2013); remember that it takes an approximately 10-mV depolarization to trigger an action potential. However, a typical neuron receives input from approximately 1,000 other neurons (Figure 2.16); because each neuron has numerous terminals, this amounts to as many as 10,000 synaptic connections in most parts of the brain and up to 100,000 in the cerebellum (Siegelbaum & Kandel, 2013).

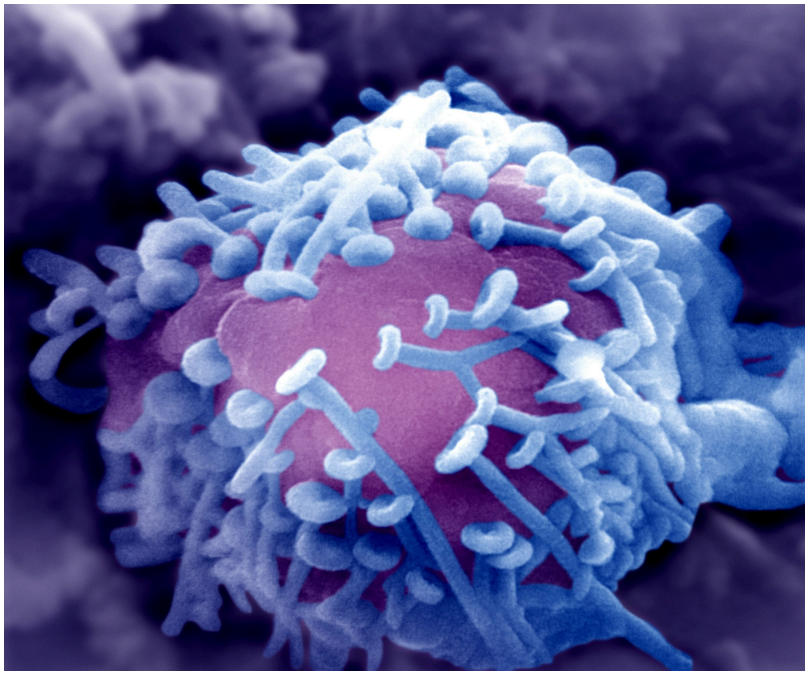
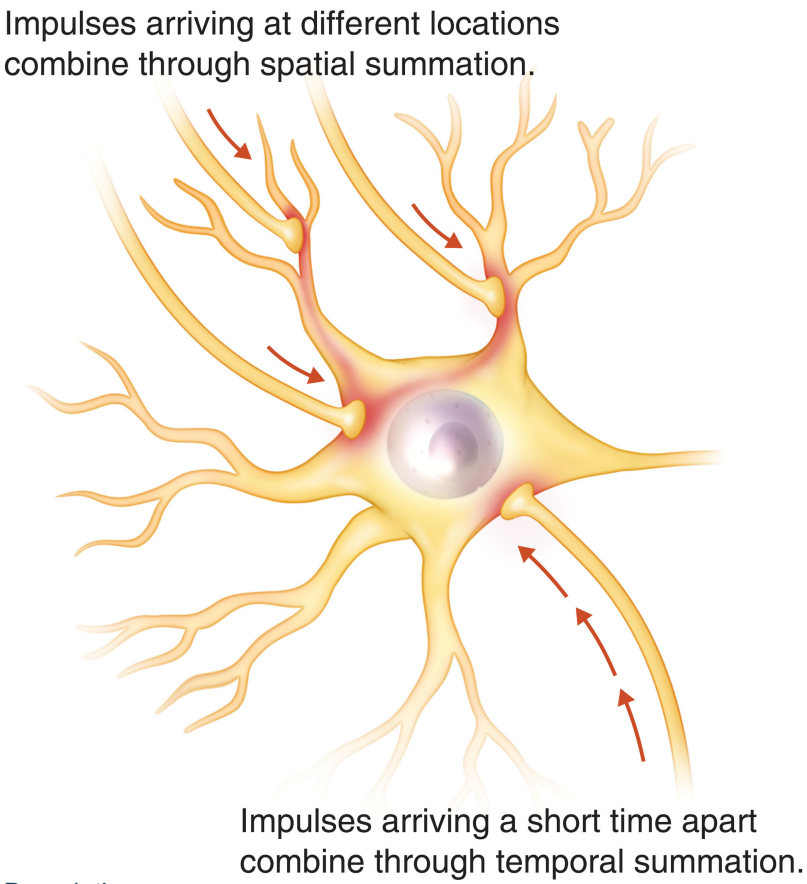


Figure 2.16 A Cell Body Virtually Covered With Axon Terminals.

SCIENCE VU, VISUALS UNLIMITED / SCIENCE PHOTO LIBRARY

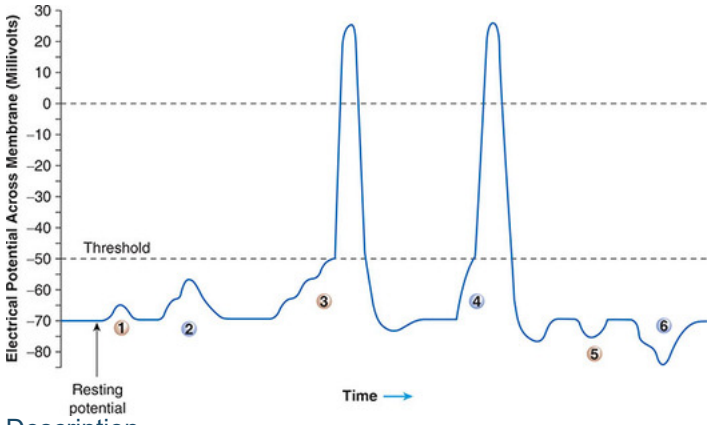
Because a single neuron has a relatively small effect, the postsynaptic neuron must combine potentials from many neurons to fire. This requirement is actually advantageous: It ensures that a neuron will not be fired by the spontaneous activity of a single presynaptic neuron, and it allows the neuron to combine multiple inputs into a more complex message. These potentials are combined at the axon hillock in two ways. **Spatial summation** combines potentials occurring simultaneously at different locations on the dendrites and cell body. **Temporal summation** combines potentials arriving a short time apart, from either the same or separate inputs. Temporal summation is possible because a local potential persists for a few milliseconds. Spatial summation and temporal summation occur differently, but they have the same result. Summation is illustrated in Figure 2.17.



Description

Figure 2.17 Spatial and Temporal Summation.

As you can see in Figure 2.18, summation combines EPSPs so that an action potential is more likely to occur. Alternatively, summation of IPSPs drives the membrane's interior even more negative and makes it more difficult for incoming EPSPs to trigger an action potential. When both excitatory and inhibitory impulses arrive on a neuron, they will summate algebraically. The combined effect will equal the difference between the sum of the partial depolarizations and the sum of the hyperpolarizations. Spatial summation of two excitatory inputs and one inhibitory input is illustrated in Figure 2.19. The effect from temporal summation would be similar.



Description

Figure 2.18 Temporal and Spatial Summation.
An EPSP (Point 1); temporal summation of two EPSPs (2); temporal summation of three EPSPs reaches threshold (3); spatial summation of EPSPs reaches threshold (4); an IPSP (5); temporal summation of two IPSPs (6).

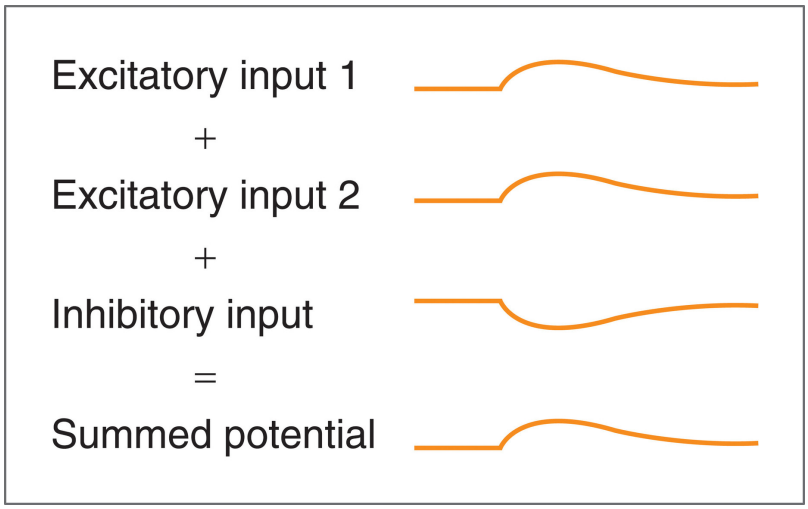


Figure 2.19 Spatial Summation of Excitatory and Inhibitory Potentials.
Note that inhibitory potentials cancel out excitatory potentials of equal strength (and vice versa).

Because the neuron can summate inputs from multiple sources, it rises above the role of a simple message conductor—it is an *information integrator*. And using that information, it functions as a *decision maker*, determining whether to fire or not. Thus, the nervous system becomes less like a bunch of electrical wires and more like a computer. In subsequent chapters, you will come to appreciate how important the synapse is in understanding how we see, how we learn, and how we succumb to mental illness.

Terminating Synaptic Activity

Usually, the transmitter must be inactivated; otherwise, it will continue to stimulate postsynaptic receptors or leak over to other synapses and interfere with their functions. Typically, transmitters are taken back into the terminals by membrane proteins called transporters in a process called **reuptake**; they are repackaged in vesicles to be used again. At some synapses, the transmitter in the cleft is absorbed by nearby astrocytes. In others, transmitters are partially broken down through a process called inactivation. The neurotransmitter acetylcholine, for example, is inactivated by the enzyme acetylcholinesterase, which splits the molecule into its components of choline and acetate. Choline is then taken back into the terminals and used to make more acetylcholine.

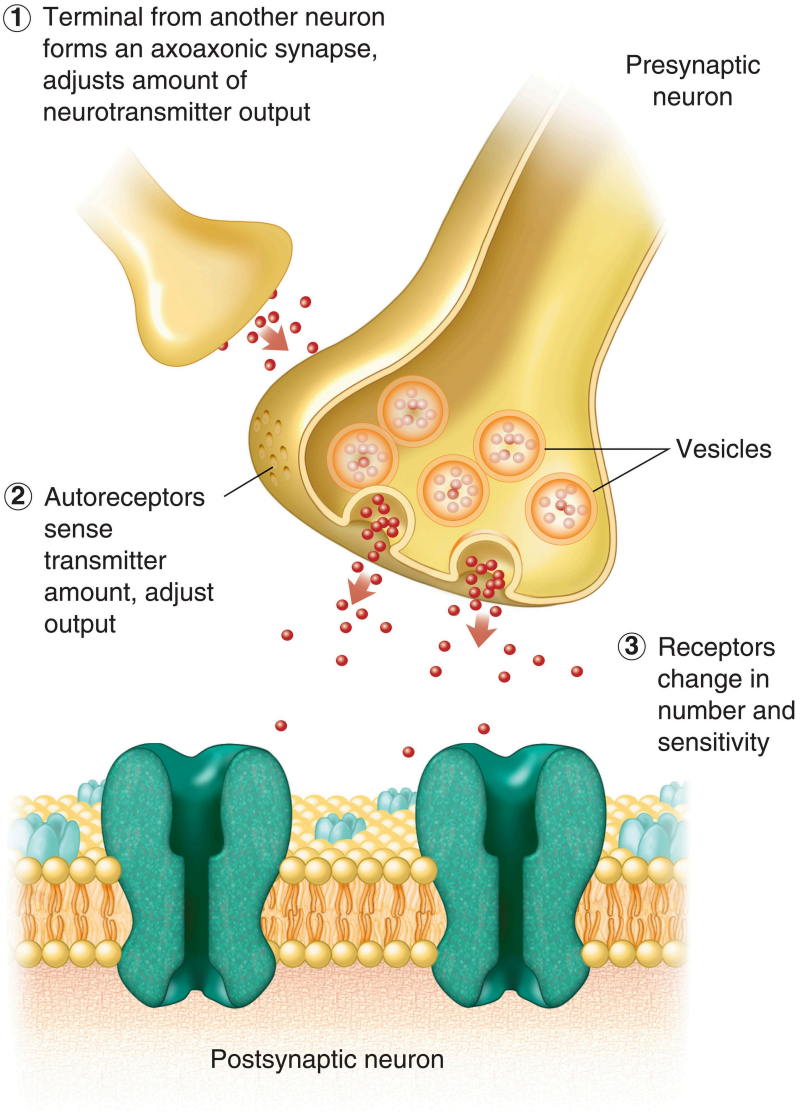
Controlling how much neurotransmitter remains in the synapse is one way to vary behavior, and many drugs capitalize on this mechanism. Cocaine blocks the reuptake of dopamine; some antidepressant medications block the reuptake of serotonin, norepinephrine, or both, whereas others (*MAO inhibitors*) prevent the enzyme monoamine oxidase from inactivating those transmitters as well as dopamine and epinephrine; and drugs for treating the muscular disorder myasthenia gravis increase acetylcholine availability by inhibiting the action of acetylcholinesterase.

Regulating Synaptic Activity

The previous description has been of a linear system that amounts to *"neuron A stimulates neuron B, neuron B stimulates neuron C,"* and so on. However, such a

simple system cannot transmit the complex information required to solve a math equation, write a symphony, or care for a newborn. Not only that, but as messages flow from neuron to neuron, activity would soon drift out of control; some activity would fade out, while other activity would escalate until it engulfed an entire area of the brain. A nervous system that controls complex behavior must have several ways to regulate its activity.

The synapses described so far are referred to as *axodendritic* and *axosomatic* synapses, because their terminals connect to dendrites and cell bodies. At *axoaxonic* synapses, a third neuron releases transmitter onto the terminals of the presynaptic neuron (see Point 1 in Figure 2.20). The result is **presynaptic excitation** or **presynaptic inhibition**, which increases or decreases, respectively, the presynaptic neuron's release of neurotransmitter onto the postsynaptic neuron. One way an axoaxonic synapse can adjust a presynaptic terminal's activity is by regulating the amount of calcium entering the terminal, which, you will remember, triggers neurotransmitter release.



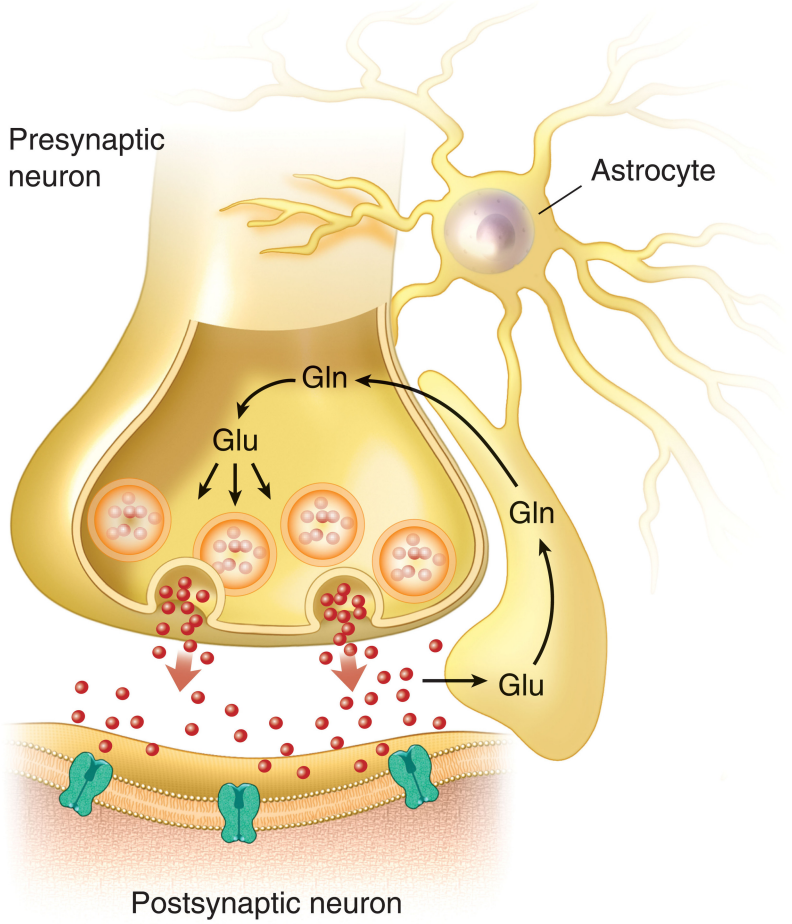
Description

Figure 2.20 Regulating Activity at the Synapse.

What are the three ways of regulating synaptic activity?

Neurons also regulate their own synaptic activity in two ways. **Autoreceptors** on the presynaptic terminals sense the amount of transmitter in the cleft; if the amount is excessive, the presynaptic neuron reduces its output (Figure 2.20, Point 2). Postsynaptic neurons participate in regulation of synaptic activity as well. When there are unusual increases or decreases in neurotransmitter release, postsynaptic receptors change their sensitivity or even their numbers to compensate (Figure 2.20, Point 3). You will find in Chapter 14 that receptor changes figure prominently in some psychological disorders, such as schizophrenia.

Glial cells also contribute to the regulation of synaptic activity. They surround the synapse and prevent neurotransmitter from spreading to other synapses, but some also remove neurotransmitter from the synaptic cleft and recycle it for the neuron's reuse (Figure 2.21). By varying the amount of transmitter they remove, glial cells influence postsynaptic excitability (Oliet, Piet, & Poulain, 2001). They can even respond to the neurotransmitter level in the synapse by releasing transmitters of their own. These gliotransmitters regulate transmitter release from the presynaptic neuron or directly stimulate the postsynaptic neuron to excite or inhibit it (M. Anderson & Hanse, 2010; Newman, 2003). Thus, rather than simply being neural "glue" as the name implies, glia should be considered active partners in neural transmission.



Description

Figure 2.21 Glial Cell Interacting With Neurons at the Synapse.
An astrocyte, a type of glial cell, encloses the synapse, where it absorbs the neurotransmitter glutamate (Glu) from the synaptic cleft. It recycles the transmitter into its precursor glutamine (Gln) and returns the Gln to the presynaptic terminal for reuse. The glial cell can influence synaptic activity by granting or withholding transmitter absorption and by releasing its own transmitter in response to the neurotransmitter level in the synapse.

Source: Adapted with permission from "Energy on Demand," by P. J. Magistretti et al., 1999, *Science*, 283, p. 497. Copyright © 1999. Reprinted with permission from AAAS.

Neurotransmitters

Table 2.2 on page 40 lists twelve transmitters, grouped according to their chemical structure. This is an abbreviated list; there are other known or suspected transmitters, and there are doubtless additional transmitters yet to be discovered. This summary is intended to illustrate the variety in neurotransmitters and to give you some familiarity with the functions of a few of the major ones. You will encounter most of them again in the discussion of various behaviors in later chapters.

Table 2.2

TABLE 2.2 Some Representative Neurotransmitters.

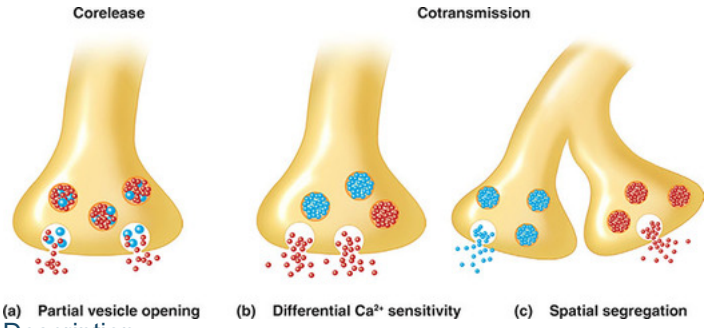
NEUROTRANSMITTER	FUNCTION
Acetylcholine	Transmitter at muscles; in brain, involved in learning, etc.
Monoamines	
Serotonin	Involved in mood, sleep and arousal, aggression, depression, obsessive-compulsive disorder, and alcoholism.
Dopamine	Contributes to movement control and promotes reinforcing effects of food, sex, and abused drugs. Dysregulation is involved in schizophrenia and Parkinson's disease.
Norepinephrine	A hormone released during stress. Functions as a neurotransmitter in the brain to increase arousal and attentiveness to events in the environment. Diminished norepinephrine transmission is involved in depression.
Epinephrine	A stress hormone related to norepinephrine; plays a minor role as a neurotransmitter in the brain.
Amino Acids	
Glutamate	The principal excitatory neurotransmitter in the brain and spinal cord. Vitally involved in learning; glutamate dysfunction is implicated in schizophrenia.
Gamma-aminobutyric acid (GABA)	The predominant inhibitory neurotransmitter. Its receptors respond to alcohol and the class of tranquilizers called benzodiazepines. Deficiency in GABA or receptors is one cause of epilepsy.
Glycine	Inhibitory transmitter in the spinal cord and lower brain. The poison strychnine causes convulsions and death by affecting glycine activity.
Neuropeptides	
Endorphins	Neuromodulators that reduce pain and enhance reinforcement.
Substance P	Transmitter in neurons sensitive to pain.
Neuropeptide Y	Initiates eating and produces metabolic shifts.
Gas	
Nitric oxide	One of two known gaseous transmitters, along with carbon monoxide. Can serve as a retrograde transmitter, influencing the presynaptic neuron's release of neurotransmitter. Viagra enhances male erections by increasing nitric oxide's ability to relax blood vessels and produce penile engorgement.

Having a variety of neurotransmitters multiplies the effects that can be produced at synapses; the fact that there are different subtypes of the receptors adds even more. For example, two types of receptors detect acetylcholine: the nicotinic receptor, so called because it is also activated by nicotine, and the muscarinic receptor, named for the mushroom derivative that can stimulate it. Nicotinic receptors are excitatory; they are found in muscles and, in lesser numbers, in the brain. Muscarinic receptors are more frequent in the brain, where they have an excitatory effect at some locations and an inhibitory one at others. Other transmitters have many more receptor subtypes than acetylcholine does.

For decades, neurophysiologists labored under the erroneous belief, known as **Dale's principle**, that a neuron was capable of releasing only a single transmitter. We now know that many neurons ply their postsynaptic partners with more than one chemical messenger (Vaaga, Borisovska, & Westbrook, 2014). These neurons may release two fast-acting neurotransmitters, a fast-acting neurotransmitter and a slow-acting monoamine, or a fast-acting neurotransmitter and a neuromodulator, which alters the effect of the transmitter. There is even evidence that some neurons release more than two neurotransmitters, for example, dopamine, gamma-aminobutyric acid (GABA), and glutamate. And some neurons can release one transmitter in response to weak stimulation and another during strong stimulation. As you can now see, chemical transmission vastly increases the complexity of the nervous system.

? What are two additional ways synapses add information complexity?

The release can occur in three ways. In *corelease*, the transmitters are packaged in the same vesicles. However, this doesn't mean they're always released equally; in the example in Figure 2.22a, the fusion pores between the vesicle and terminal membranes have opened only partially, impeding the release of the larger messenger molecules while allowing the smaller molecules to exit freely (see M. Braun et al., 2007). In *cotransmission*, the transmitters are in separate vesicles. Vesicles containing different transmitters in the same terminal differ in sensitivity to calcium (Ca^{2+}); a low rate of neural impulses will trigger release of only one of the messengers, whereas a higher rate will release both of them (Figure 2.22b). Finally, the neuron may release different transmitters from its various terminals to produce different effects at separate destinations (Figure 2.22c).



Description

Figure 2.22 Neural Corelease and Cotransmission.
(a) In corelease, the neuron can limit exit of larger chemical messengers by partially opening the fusion pore. (b) When the messengers are in different vesicles in the same terminal, the vesicles' differential Ca^{2+} sensitivity provides release selectivity. (c) Packaging the transmitters in separate terminals allows the neuron to have different effects at the terminals' destinations.

Source: Adapted from "Dual-transmitter Neurons: Functional Implications of Co-release and Co-transmission," by C. E. Vaaga, M. Borisovska, and G. L. Westbrook, 2014, *Current Opinions in Neurobiology*, 29, 25–32.

Corelease and cotransmission are not well understood, but we do know they play a significant role in neural functioning. For example, release of inhibitory GABA dampens the excitatory effects of glutamate during seizures (Trudeau, 2004) and counters the arousing effects of histamine to prevent hyperactivity and sustained wakefulness (Yu et al., 2015). In addition, direction-detecting cells in the retina of the eye release acetylcholine and GABA in response to any movement of a visual object, but they release only GABA when the movement is in the cell's "preferred" direction (S. Lee, Kim, & Zhou, 2010).

A Further Look:

Agonists and Antagonists in the Real World

Amazonians tip their blowgun darts with the plant neurotoxin curare.

Source: By Jialiang Gao, https://commons.wikimedia.org/wiki/File:Yahua_Blowgun_Amazon_Iquitos_Peru.jpg, licensed under CC BY-SA 4.0 https://creativecommons.org/licenses/by-sa/4.0/.

Neurotransmitters are not the only substances that affect the nervous system. The many drugs and other compounds that mimic or increase the effect of a neurotransmitter are called **agonists**. Any substance that reduces the effect of a neurotransmitter is called an *antagonist*. Practically all drugs that have a psychological effect interact with a neurotransmitter system in the brain, and many of them do so by mimicking or by blocking the effect of neurotransmitters (S. H. Snyder, 1984).

You have already seen that the effect of acetylcholine (ACh) is duplicated by nicotine and muscarine at the two kinds of acetylcholine receptors (nicotinic-ACh and muscarinic-ACh, respectively). Opioid drugs such as heroin and morphine also act as agonists, stimulating receptors for opiate-like transmitters in the body. The drugs naloxone and naltrexone act as antagonists to opiates, occupying the receptor sites without activating them; consequently, naloxone and naltrexone can be used to counteract an overdose. The plant toxin curare blocks nicotinic acetylcholine receptors at the muscle, causing paralysis (A. Trautmann, 1983). Indigenous tribes of Central and South America put curare on the tips of their darts and arrows to disable their game. A synthetic version of curare was used as a muscle relaxant during surgery before safer and more effective drugs were found (M. Goldberg & Rosenberg, 1987). It was even used occasionally in the past to treat the muscle spasms of tetanus (lockjaw), which, ironically, is caused by another neurotoxin.

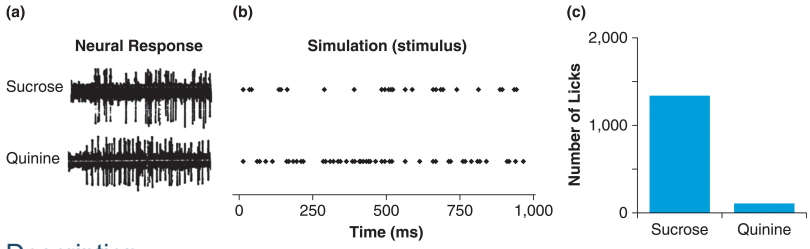
Neural Codes and Neural Networks

Underlying this discussion has been the assumption that we can explain behavior by understanding what neurons do. But we cannot make good on that promise as long as we talk as if neural communication is limited to single chains of neurons that either fire or don't fire. In fact, neurons are capable of generating complex messages, which they send across intricate networks.

Coding of Neural Messages

Neurons don't just produce a train of equally spaced impulses: They vary the intervals between spikes, they produce bursts of varying lengths, and the bursts can be separated by different intervals (Cariani, 2004). But do these temporal (time-related) variations in firing pattern form a code that the brain can use, or are they just "noise" in the system? The best way to answer this question is to look at sensory processes,

because the researcher can correlate firing patterns with sensory input on one end and behavior on the other. A good example is an early study done by Patricia Di Lorenzo and her colleague Gerald Hecht (1993). First, they recorded the firing patterns in individual taste neurons of rats during stimulation with a sucrose (sugar) solution and quinine (the flavoring in tonic water). As you can see in Figure 2.23a, these flavors produce different neural activity. Then they duplicated the temporal patterns in the form of electrical pulses (Figure 2.23b) and used these to stimulate the taste pathways of other rats. The assumption was that if the brain *uses* this information, the unanesthetized rats would behave as if they were actually *tasting* sweet sucrose or bitter quinine. As Figure 2.23c shows, that is exactly what happened: The rats licked a water tube at a high rate when they were receiving stimulation patterned after sucrose but almost stopped licking—even though they were water deprived—when the stimulation was patterned after quinine.



Description

Figure 2.23 Response of Rats to Neural Stimulation Simulating the Taste of Sucrose and Quinine.
(a) Recordings from individual neurons during stimulation with sucrose and quinine. (b) Electrical stimulation mimicking the recorded neuronal activity: Each dot represents a signal neural impulse. (c) The average number of times the rats licked a drinking tube for water during delivery of the quinine simulation and the sucrose simulation.

Sources: (a) and (b) Adapted from Figure 7 of "Temporal Coding in the Gustatory System," by R. M. Hallock and P. M. Di Lorenzo, 2006, *Neuroscience and Biobehavioral Reviews*, 30, p. 1156. Used with permission from Elsevier. (c) Adapted from Figure 4 of "Perceptual Consequences of Electrical Stimulation in the Gustatory System," by P. M. Di Lorenzo and G. S. Hecht, 1993, *Behavioral Neuroscience*, 107, p. 135.

However, this coding apparently is not sufficient to carry the complex information involved in brain communication. An additional opportunity for coding is provided by the fact that neural information often travels over specialized pathways. For example, taste information is carried by at least five types of specialized fibers; Di Lorenzo and Hecht (1993) recorded the sucrose firing pattern from a "labeled line" specialized for sweet stimuli and the quinine pattern from another specialized for bitter stimuli. In later chapters, you will see that not only taste but also information about color and about the higher sound frequencies is transmitted over a limited number of labeled lines. However, even with temporal coding and labeled lines, a significant burden remains for the brain if it is to make sense of this information. This leads us to the topic of neural networks.

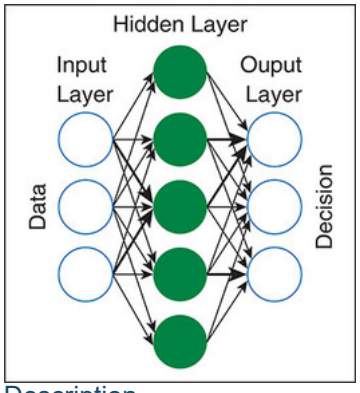
Neural Networks

Individual neurons cannot carry enough information to determine the taste of a bite of food or the color of an object. Color processing, for example, depends on four "labeled lines" carrying information about red, green, blue, and yellow light; we can distinguish millions of colors by comparing the relative activity in these four pathways. This kind of analysis requires complex interactions among a network of neurons. **Neural networks** are groups of neurons that function together to carry out a process; they are where the most complex neural processing—the "computing" work of the brain—occurs. Sometimes these networks involve a relatively small number of neurons in a single area, such as groups of neurons in a part of the brain called the

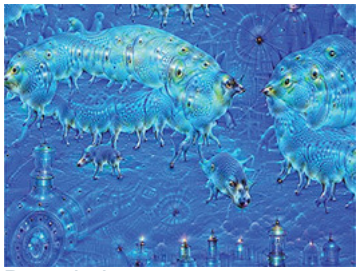
hippocampus. When rats navigate a maze, these networks store their preceding choices and calculate their next choice. The networks perform so reliably that the researcher can use their activity to predict which way the rat will turn after a delay (Pastalkova, Itskov, Amarasingham, & Buzsáki, 2008). As you will see in later chapters, other networks combine the activity of widespread brain areas to perform language functions (Chapter 9), to identify an object visually and locate it in space (Chapter 10), and, some researchers believe, to produce conscious awareness (Chapter 15). We go into more detail about other uses of neural networks, such as in the creation of art and in deceptive video editing, in A Further Look.

A Further Look:

Uses and Abuses of Artificial Neural Networks



Description


Description

Left: Example of a simple artificial neural network. Right: DeepDream image produced from a picture of jellyfish after 50 iterations, by a network trained on pictures of dogs.

Custom art (G Hough, 2019)

Artwork by Martin Thoma (2015, Creative Commons Public Domain)

Artificial neural networks are computer programs that mimic the brain's neural networks; rather than being programmed to perform in a specific way, these networks *learn* how to carry out their task by trial and error, much as we do. The networks consist of multiple layers of simulated neurons: an input layer, one or more hidden layers where the processing is done, and an output layer. The network is trained by repeatedly feeding it data, then giving it correct results to compare with its own output. At first, the network's performance is random, but it improves over time by adjusting the strength of connections among its simulated neurons. For example, an early network that was designed to read and speak English text initially produced random sounds, which were replaced with babbling and then pseudowords, but after just 10 training trials, the speech was intelligible and sounded like a small child's (Sejnowski & Rosenberg, 1987).

Artificial neural networks can be used to identify people through face recognition, control a self-driving car, or detect alterations to an image or video (Coldeway, 2019). They are especially useful in tasks requiring decision making, such as in finance, but also as far afield as in art. *DeepDream* software, which was created to recognize faces and other patterns in images, can be run in reverse to produce “psychedelic” and surreal art. The two photographs here were created from a picture of jellyfish by a network that was trained to perceive dogs, so it gave the jellyfish image “dog” characteristics.

But anything this powerful is subject to abuse; a good example is *deepfake* videos. These originated as fake pornographic videos of celebrities, created by collecting multiple photos of the person from around the web and superimposing them on the body of an actor. More recently, a deepfake video appearing to show Facebook’s Mark Zuckerberg saying he has “total control of billions of people’s stolen data” went viral on the web. The frightening potential exists to create convincing fake evidence of a person committing a crime or a video of a political opponent making reprehensible statements. As a means of warning about the risks of such “fake news,” director Jordan Peele and BuzzFeed CEO Jonay Peretti created a deepfake video of Barack Obama calling Trump a “complete and utter dips__t” (Chivers, 2019).

Understanding these networks is the next big frontier in brain research. Their complexity and relative inaccessibility are challenging researchers’ resolve and ingenuity, but developments in brain-imaging capabilities make the goal more realistic. The **Human Connectome Project** is a large-scale, multi-university effort to map the brain’s circuits. Its researchers are using a combination of four scanning techniques, behavioral measures, and genetic analysis to determine the brain’s anatomical and functional connectivity (Van Essen et al., 2013). The maps will help researchers understand normal brain functioning in realms such as learning and consciousness, as well as disorders in functioning, including autism and schizophrenia (Figure 2.24). By the way, it took more than a decade to map the roundworm’s brain, with just 300 neurons and 7,000 connections, so attempting it for the human brain is a very tall order.

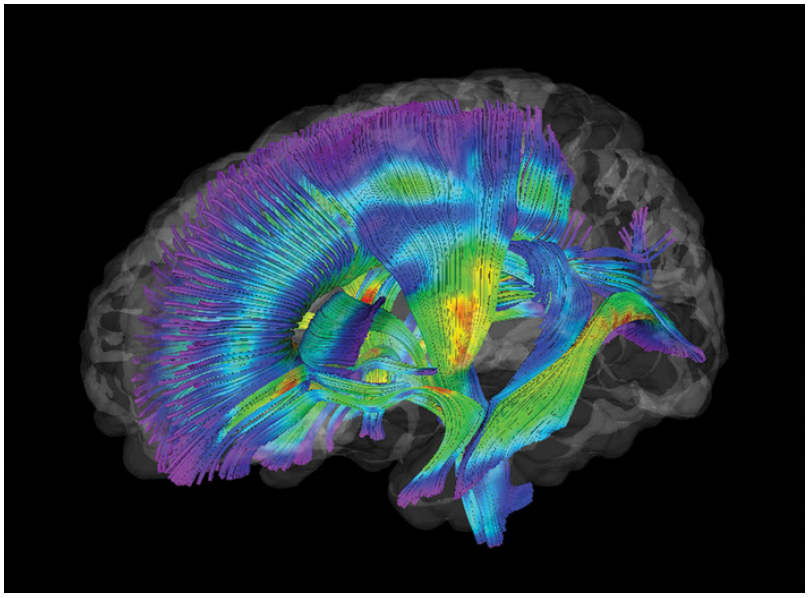


Figure 2.24 Image of White Matter Fiber Tracts.
This image is from the brain of an infant at risk for autism, based on having older siblings with autism. Those who were diagnosed with autism at 24 months had already begun to differ in tract development by the age of 6 months (Wolff et al., 2012). The study used a white matter imaging technique called diffusion tensor imaging; colors represent varying strengths of connection.

Source: Jason Wolff, PhD, University of North Carolina at Chapel Hill.

While we're waiting for neuroscientists to explain how the brain works, the idea of neural networks provides a useful way of thinking about mental processes. The next time you are trying to remember a person's name that is "on the tip of your tongue," imagine your brain activating individual components of a neural network until one produces the name you're looking for. If you visualize the person's face as a reminder, imagine that the name and the image of the face are stored in connected networks, so that activating one memory activates the other. This is not just speculation: Electrode recordings from patients preparing for brain surgery show that the information triggered by the photo of a familiar person and by the person's written name converge on the same neurons in a critical memory area of the brain (Quian Quiroga, Kraskov, Koch, & Fried, 2009)—thanks, of course, to neural networks.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- How is information transmitted at the synapse?
- It can be said that integration transforms neurons from a "telephone line" into a computer. Explain.
- What difference would it make if there were no regulation of activity at the synapse?
- What is Dale's principle, and in what way is it incorrect?
- Explain why researchers' focus is shifting from localized neural activity to brainwide connections and activity.
- What are artificial neural networks?

IN PERSPECTIVE

It is impossible to understand either the brain or behavior without first knowing the capabilities and the limitations of the neuron. Although more complexity is added at the synapse, a relatively simple device is the basis for our most sophisticated capabilities and behaviors. However, what happens at the individual neuron is not enough to account for human behavior; neurons work in concert with each other, in both local and brainwide networks. With modern tools and large cooperative efforts, researchers hope to understand how neurons work together to produce thought, memory, emotion, and consciousness. In Chapter 3, you will learn about some of the functional structures in the brain that are formed by the interconnection of neurons.

Chapter Summary

The Cells That Make Us Who We Are

- There are three major kinds of neurons: motor neurons, sensory neurons, and interneurons. Although they play different roles, they have the same basic components and operate the same way.
- The neural membrane is electrically polarized. This polarity is the resting potential, which is maintained in the short term by the effects of selective membrane permeability in combination with the forces of diffusion and electrostatic pressure and in the long term by the sodium-potassium pump.
- Polarization is the basis for the neuron's responsiveness to stimulation, in the form of the graded potential and the action potential.
- The neuron is limited in firing rate by the absolute refractory period and in its ability to respond to differing strengths of stimuli by the all-or-none law. More intense stimuli cause the neuron to fire earlier during the relative refractory period, providing a way to encode stimulus intensity (the rate law).
- Glial cells provide the myelination that enables neurons to conduct rapidly while remaining small. They also help regulate activity in the neurons and provide several supporting functions for neurons.

How Neurons Communicate With Each Other

- Transmission from neuron to neuron is usually chemical in vertebrates, involving neurotransmitters released onto receptors on the postsynaptic dendrites and cell body.
- The neurotransmitter can create an excitatory postsynaptic potential, which increases the chance that the postsynaptic neuron will fire, or it can create an inhibitory postsynaptic potential, which decreases the likelihood of firing.
- Through temporal and spatial summation, the postsynaptic neuron integrates its many excitatory and inhibitory inputs.
- Regulation of synaptic activity is produced by axoaxonic synapses from other neurons, adjustment of transmitter output by autoreceptors, and change in the number or sensitivity of postsynaptic receptors.
- Leftover neurotransmitter may be taken back into the presynaptic terminals, absorbed by glial cells, or broken down by an enzyme.
- The human nervous system contains a large number of neurotransmitters, which are detected by an even greater variety of receptors. A neuron can release combinations of two or more neurotransmitters.
- The computing work of the brain is done in complex neural networks.

Study Resources

For Further Thought

- What would be the effect if there were no constraints on the free flow of ions across the neuron membrane?
- What effect would it have on neural conduction if the action potential were decremental?
- Sports drinks replenish electrolytes that are lost during exercise. Electrolytes are compounds that separate into ions; for example, sodium chloride (table salt) dissociates into sodium and chloride ions. What implication do you think electrolyte loss might have for the nervous system? Why?
- Imagine what the effect would be if the nervous system used only one neurotransmitter.
- How similar to humans do you think computers are capable of becoming? How much is your answer based on how you think human behavior is controlled versus how capable you think computers are?

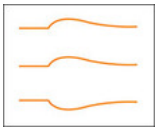
Test Your Understanding

1. Describe the ion movements and voltage changes that make up the neural impulse, from graded potential (at the axon hillock) to recovery.
2. Discuss the ways in which the synapse increases the neuron's capacity for transmitting information.
3. Describe how neurons regulate neurotransmitter amounts in the synapse and what might happen to behaviors if those processes work too well or too poorly.
4. Describe neural networks and explain their importance.

Select the best answer:

1. The inside of the neuron is relatively poor in _____ ions and rich in _____ ions.
    1. chloride, phosphate
    2. sodium, potassium
    3. potassium, sodium
    4. calcium, sodium
2. The rate law
    1. explains how the intensity of stimuli is represented.
    2. does not apply to neurons outside the brain.
    3. describes transmission in myelinated axons.
    4. describes the process of postsynaptic integration.
3. Without the sodium-potassium pump, the neuron would become
    1. more sensitive because of accumulation of sodium ions.
    2. more sensitive because of accumulation of potassium ions.
    3. overfilled with sodium ions and unable to fire.
    4. overfilled with potassium ions and unable to fire.
4. There is a limit to how rapidly a neuron can produce action potentials. This is due to
    1. inhibition.
    2. facilitation.
    3. the absolute refractory period.
    4. the relative refractory period.
5. Saltatory conduction results in
    1. less speed with the use of more energy.
    2. greater speed with the use of less energy.
    3. less speed with the use of less energy.
    4. greater speed with the use of more energy.
6. General anesthetics open potassium channels, allowing potassium ions to leak out of the neuron. This
    1. increases firing in pain-inhibiting centers in the brain.
    2. increases firing in the neuron until it is fatigued.
    3. depolarizes the neuron, preventing firing.
    4. hyperpolarizes the neuron, preventing firing.

7. When the action potential arrives at the terminal button, entry of _____ ions stimulates release of transmitter.
    1. potassium
    2. sodium
    3. calcium
    4. chloride
8. All the following neurotransmitters are deactivated by reuptake except
    1. acetylcholine.
    2. norepinephrine.
    3. serotonin.
    4. dopamine.
9. An inhibitory neurotransmitter causes the inside of the postsynaptic neuron to become
    1. more positive.
    2. more negative.
    3. more depolarized.
    4. neutral in charge.
10. Excitatory postsynaptic potentials are typically produced by movement of _____ ions, whereas inhibitory postsynaptic potentials are typically produced by movement of _____ ions.
    1. potassium; sodium or chloride
    2. potassium; sodium or calcium
    3. sodium; calcium or chloride
    4. sodium; potassium or chloride
11. Which of the following is not an example of regulation of synaptic activity?
    1. A neuron has its synapse on the terminals of another and affects its transmitter release.
    2. Autoreceptors reduce the amount of transmitter released.
    3. A presynaptic neuron inhibits a postsynaptic neuron.
    4. Postsynaptic receptors change in numbers or sensitivity.
12. The graph below shows three graded potentials occurring at the same time.

    Assume that the resting potential is –70 mV and that each graded potential individually produces a 5-mV change. What is the membrane's voltage after the graded potentials arrive?

    1. –65 mV
    2. –70 mV
    3. –75 mV
    4. +75 mV
13. The presence of synapses in a neuron chain provides the opportunity for
    1. increases in conduction speed.
    2. modification of neural activity.
    3. two-way communication in a pathway.
    4. regeneration of damaged neurons.
14. Neural networks
    1. are groups of neurons that function together.
    2. are where the most complex work of the brain occurs.
    3. must connect at least two brain areas to be considered a network.
    4. All of these are true.
    5. Not all of these are true.

Answers:

1. b, 2. a, 3. c, 4. c, 5. b, 6. d, 7. c, 8. a, 9. b, 10. d, 11. c, 12. a, 13. b, 14. e.

For Further Reading

1. *Synaptic Self*, by Joseph LeDoux (Penguin Books, 2003), takes the position that "your 'self,' the essence of who you are, reflects patterns of interconnectivity between neurons in your brain." A good read by a noted neuroscientist.
2. "Astrocyte Regulation of Synaptic Behavior," by Nicola J. Allen (*Annual Review of Cell and Developmental Biology*, 2014, *30*, 439–463), synthesizes research on astrocytes' role in synapse formation and regulation of synaptic activity.
3. "From Cajal to Connectome and Beyond" (*Annual Review of Neuroscience,* 2016, *39,* 197–216) reviews the "long history of attempts to understand how the brain operates as a system," dating as far back as the fifth century.
4. Two books by Olaf Sporns, *Discovering the Human Connectome* (MIT Press, 2016) and *Networks of the Brain* (MIT Press, 2016), elaborate on topics in this chapter.
5. Sebastian Seung's book *Connectome* (Mariner Books, 2013) describes the effort to map the brain using computers and artificial intelligence; you can read a summary and review in *New Scientist*, February 4, 2012, p. 46.
6. "A Million Spiking-Neuron Integrated Circuit With a Scalable Communication Network and Interface" (*Science,* 2014, *345,* 668–673) describes an IBM/Cornell University project's brain-inspired 5.4-billion transistor computer chip that mimics 1 million neurons and 256 million synapses. As a result, it can perform human-like operations, such as analyzing video to identify people and objects.
7. *Beautiful Brain: The Drawings of Santiago Ramón y Cajal* (Abrams, 2017), by Larry Swanson, Eric Newman, et al., presents Cajal's drawings as beautiful art in their own right.

Key Terms

absolute refractory period 30

action potential 27

agonist 42

all-or-none law 29

antagonist 42

autoreceptor 39

axon 22

axon terminal 22

cell body 22

Dale's principle 40

dendrites 22

electrostatic pressure 26

excitatory postsynaptic potential (EPSP) 35

force of diffusion 26

glial cell 30

graded potential 29

Human Connectome Project 44

hyperpolarization 34

inhibitory postsynaptic potential (IPSP) 35

interneuron 24

ion 25

ionotropic receptor 34

metabotropic receptor 34

motor neuron 22

myelin 30

neural network 43

neuron 22

neurotoxin 28

neurotransmitter 23

node of Ranvier 31

nondecremental 29

oligodendrocyte 30

optogenetics 28

partial depolarization 34

polarization 25

postsynaptic 33

presynaptic 33

presynaptic excitation 38

presynaptic inhibition 38

rate law 30

relative refractory period 30

resting potential 25

reuptake 38

saltatory conduction 31

Schwann cell 31

sensory neuron 24

sodium-potassium pump 26

spatial summation 37

synapse 33

synaptic cleft 33

temporal summation 37

vesicle 33

voltage 25

Descriptions of Images and Figures

Back to Figure

The neuron consists of the cell body with a nucleus. Dendrites are extensions branching from the cell body. Axon is a tail-like structure, extending from the axon hillock on the cell body and wrapped in a discontinuous myelin sheath. The axon end branches into multiple terminals that are attached to muscle fibers. Arrows point from axon hillock to the terminals.

Back to Figure

1. Unipolar or sensory neuron: The neuron consists of the cell body with a nucleus in it. One side of the cell body splits into dendrites and axons. The dendrites penetrate the skin from the inside and extend till the skin surface. The axon extends in the opposite direction, and its end branches into terminals. Arrows point from dendrites to axon terminals.
2. Bipolar or sensory neuron: The neuron consists of the cell body with a nucleus in it. Dendrites extend from one side of the body and axon extends from the other side. The end of the axon branches into terminals. Arrows point from dendrites to axon terminals.
3. Interneuron: The neuron consists of a cell body with a nucleus in it. Dendrites extend in all directions from the cell body.

Back to Figure

In the illustration, an intracellular microelectrode is inserted into the body of a neuron. The intracellular microelectrode and a reference microelectrode are connected to an amplifier, which in turn is connected to a computer. The computer screen displays a graph.

The micrograph shows the tip of a microelectrode approaching the body of a neuron.

Back to Figure

The illustration shows channels embedded in the lipid bilayer membrane. The extracellular fluid consists mostly of positive sodium ions, some negative chloride ions, and few positive potassium ions. The intracellular fluid consists mostly of positive potassium ions and negative organic anions, some negative chloride ions, and a few positive sodium ions.

Back to Figure

In the graph, the vertical axis is labeled electric potential in millivolts, and ranges from negative 80 to positive 30 in increments of 10. The threshold is negative 60. The potential is initially constant at negative 70, and this is the resting potential. The potential increases to negative 60 in a concave down manner, and this corresponds to local potential. The potential then increases sharply to 25, corresponding to action potential. During repolarization, the potential drops to negative 80 in a concave up manner, which then rises slowly to negative 70 in a concave down manner while returning to resting potential.

A set of four illustrations show sodium channel and ions in red and potassium channel and ions in blue. The text under each illustration is as follows. a. Resting potential and local potential: Sodium channels (red) and potassium channels (blue) are closed and the membrane is at resting potential. Arrival of a local potential partially depolarizes the membrane but does not cause the channels to open unless it reaches threshold. b. Action potential: As the local potential reaches the neuron’s

threshold, the sodium channels' activation gates open. Sodium ions (red) rush in, producing an action potential. The membrane in that area depolarizes and overshoots to positive. c. Repolarization: Sodium channels' inactivation gates close. Potassium channels' activation gates open; potassium ions (blue) move out, repolarizing the membrane. Polarity overshoots beyond resting potential. d. Return to resting potential: Potassium channels close. The "excess" displaced ions drift away and the potential returns to resting level. (The sodium channel gates will return to their original state later.)
Back to Figure

The horizontal axis is labeled Training days, and lists baseline, 1, 2, 3, and 4. The vertical axis is labeled percentage of freezing, and ranges from 0 to 40 in increments of 10. Freezing is the fear response by mice. The approximate data from the graph are tabulated below.

Back to Figure

The illustration shows a neural impulse traveling along the axon of a presynaptic neuron. The impulse reaches the terminals, which are in contact with the dendrites of the postsynaptic neuron. An accompanying illustration shows a magnified view of the synaptic cleft between the axon terminal of a presynaptic axon and dendrite of the postsynaptic neuron.

Back to Figure

The illustration shows two hearts. An electrode is in contact with the accelerator nerve attached to the first heart. The second heart is injected with a liquid. Before stimulation, the heart rate was normal. The heart rate increases during stimulation and after liquid is added.

Back to Figure

Impulses traveling along the terminals arrive a short time apart and at different locations. Text reads, Impulses arriving at different locations combine through spatial summation. Impulses arriving a short time apart combine through temporal summation.

Back to Figure

The horizontal axis is labeled time. The vertical axis is labeled electric potential across membrane, and ranges from negative 80 to 30 in increments of 5. The graph labels six points occurring at major inflections. All data are approximate. The potential is negative 70, increases to negative 75 at point 1, decreases, increases to negative 57 at point 2, decreases, increases sharply to 26 at point 3, decreases sharply, increases sharply to 26 at point 4, decreases, decreases to negative 74 at point 5, increases, and decreases to negative 85 at point 6.

Back to Figure

There are three stages in the regulation of activity:

1. Terminal from another neuron forms an axoaxonic synapse and adjusts the amount of transmitter output.
2. Autoreceptors on the presynaptic neuron sense transmitter amount and adjust the output. Neurotransmitters from the vesicles are released into the synaptic cleft.
3. Receptors in the postsynaptic neuron change in number and sensitivity.

Back to Figure

The dendrites of the astrocyte are in contact with the presynaptic neuron, and one of the dendritic branches extend to the synaptic cleft. The neurotransmitter glutamate (G l u) released by the vesicles in the presynaptic neuron into the synapse toward the receivers in the postsynaptic neuron are absorbed by the astrocyte. The astrocyte

converts glutamate into glutamine (G l n), and transfers it to the presynaptic neuron, where glutamine is converted to glutamate and is collected inside the vesicles.
Back to Figure

1. Corelease: Partial vesicle opening. Molecules of different sizes are packed in a vesicle. When the vesicle opens partially at the terminal, only smaller-sized molecules are released.
2. Cotransmission: Differential C a 2 positive (positive calcium ion) sensitivity. There are two types of molecules, with each type contained in different vesicles. At the terminal, the vesicles release molecules of a particular type.
3. Cotransmission: Spatial segregation. Each type of transmitter is packed in vesicles and is at separate terminals. The transmitters released from the vesicles at each terminal have different locations.

Back to Figure

1. Neural response: The graphs show sharp peaks and troughs, represented by lines. The neural response during stimulation by quinine shows more peaks and troughs than the neural response during stimulation by sucrose.
2. Simulation or stimulus: The horizontal axis is labeled time in milliseconds, and ranges from 0 to 1,000 in increments of 250. The graph shows two rows of dots, one for sucrose and one for quinine. There are more dots for quinine than for sucrose.
3. The horizontal axis lists sucrose and quinine and the vertical axis is labeled Number of licks, ranging from 0 to 2,000 in increments of 500. The approximate data from the graph are tabulated below.

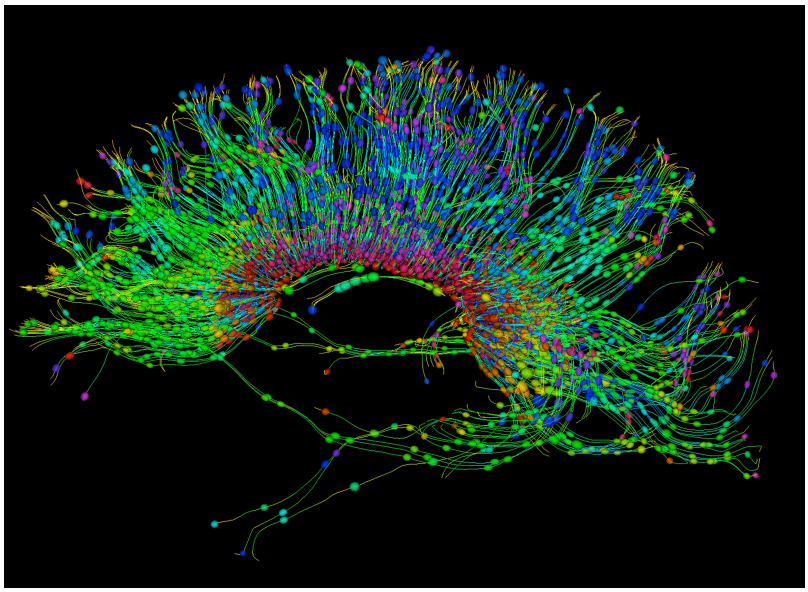
Back to image

The illustration of artificial neural network consists of three layers: The input layer, corresponding to data, represented by three circles; the hidden layer represented by five circles; and the output layer, corresponding to decision, represented by three circles. The illustration shows a dense network of arrows that point from the circles of the input layer to the circles of the hidden layer, and from the circles of the hidden layer to the circles of the output layer. Few arrows are thicker than the others.

Back to image

The DeepDream image shows a psychedelic image of a jellyfish with short tentacles located above minaret-like structures.

3 THE ORGANIZATION AND FUNCTIONS OF THE NERVOUS SYSTEM



Callista Images/Cultura/Getty Images

The Central Nervous System

The Forebrain

A Further Look | The Case of Phineas Gage

The Midbrain and Hindbrain

The Spinal Cord

Protecting the Central Nervous System

Concept Check

The Peripheral Nervous System

The Cranial Nerves

The Autonomic Nervous System

Concept Check

Development and Change in the Nervous System

The Stages of Development

A Further Look | Microtubules Move Neurons Along Their Way

How Experience Modifies the Nervous System

A Further Look | Building a Better Brain

Damage and Recovery in the Central Nervous System

A Further Look | Ultrasound Surgery

Concept Check

A Further Look | Mending the Brain With Computer Chips

In Perspective

Chapter Summary

Study Resources

After reading this chapter, you will be able to

3.1 Identify the components of the central nervous system.

3.2 Name the structures in the forebrain, midbrain, and hindbrain.

3.3 Predict how damage to specific brain structures will impact specific behaviors.

3.4 Describe the components that protect the brain from damage.

3.5 Examine the functions of the peripheral nervous system divisions.

3.6 Explain how the peripheral and central nervous systems interact in generating experiences and behavior.

3.7 Summarize the changes that the nervous system undergoes during typical development.

3.8 Illustrate the changes that occur in the nervous system as the result of experience.

Karen is a college graduate and holds a job with considerable responsibility. She is married and leads a normal life except for occasional epileptic seizures. When her doctors ordered a brain scan to find the cause of her seizures, they were astounded. The normal person's brain has many folds on its surface, so it is wrinkled like a walnut; Karen's is perfectly smooth, like the one on the right in Figure 3.1. Notice, too, that the dark areas in the middle of the brain (ventricles) are enlarged, indicating a deficiency in the amount of brain tissue. People with her disorder are usually not only *lissencephalic* (literally, *smooth-brained*) and epileptic like Karen but severely impaired intellectually as well (Barinaga, 1996; Eksioglu et al., 1996). So what really amazed Karen's doctors was not how abnormal her brain is but that she lived past

childhood and that she functions not just normally but well above average. How do we explain why some people are able to escape the consequences of what is usually a devastating developmental error? The answer is that we do not know why; it is one of the mysteries that neuroscientists are attempting to solve in order to understand the brain's remarkable resilience.

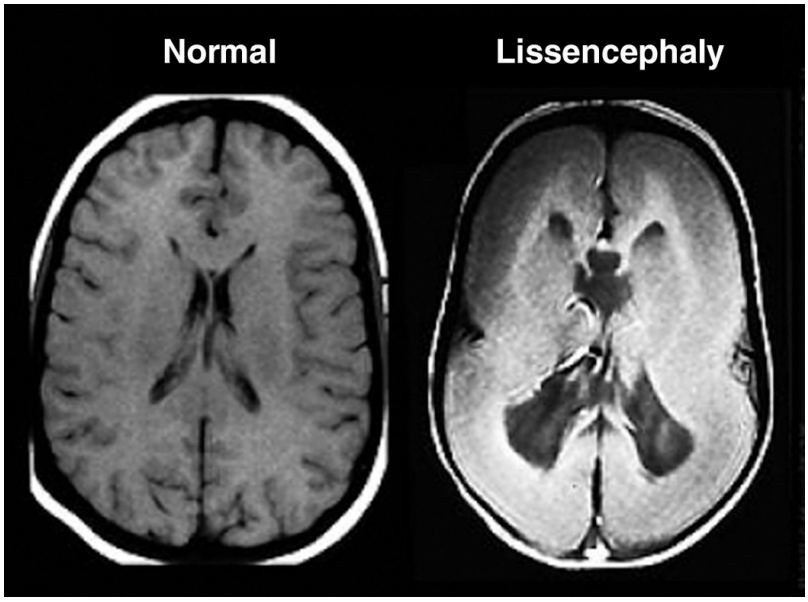


Figure 3.1 A Normal Brain and a Lissencephalic Brain.

Source: Courtesy of Dr. Joseph Gleeson, University of California San Diego School of Medicine.

You are now well versed in the functioning of neurons and how they interact with each other. What you need to understand next is how neurons are grouped into the functional components that make up the nervous system. In the next few sections, we will review the physical structure of the nervous system so that you will have a road map for more detailed study in later chapters. We will also include an overview of major functions to prepare you for the more detailed treatments to come in later chapters. First, we will look at the two divisions of the nervous system before turning our attention to issues such as brain development and change.

THE CENTRAL NERVOUS SYSTEM

The nervous system is divided into two subsystems. The **central nervous system (CNS)** includes the brain and the spinal cord. The second part is the peripheral nervous system (PNS), which we will examine later in the chapter. Before we go any further, we need to be sure you understand a couple of terms correctly. As we talk about the nervous system, be careful not to confuse *nerve* and *neuron*. A neuron is a single neural cell; a **nerve** is a bundle of axons (the long processes extending from neurons' cell bodies) running together like a multiwire cable. However, the term *nerve* is used only in the peripheral nervous system; inside the CNS, bundles of axons are called **tracts**. Most of the neurons' cell bodies are also clustered in groups; a group of cell bodies is called a **nucleus** in the CNS and a **ganglion** in the PNS. Table 3.1 should help you keep these terms straight.

Table 3.1
TABLE 3.1 Terms for Axons and Cell Bodies in the Nervous System.

	PERIPHERAL	CENTRAL
Bundle of axons	Nerve	Tract
Group of cell bodies	Ganglion	Nucleus

Figure 3.2 is a photograph of a human brain. It will be easier to visualize the various structures of the brain if you understand that the CNS begins as a hollow tube and preserves that shape as it develops (Figure 3.3). The upper end of the tube develops three swellings, which will become the forebrain, midbrain, and hindbrain; the lower part of the tube develops into the spinal cord. The forebrain appears to be perched on top of the lower structures as it enlarges and almost completely engulfs them. By comparing the four drawings in this series, you can see that the mature forebrain obscures much of the lower brain from view. You will get a better idea of these hidden structures later when we look at an interior view of the brain.

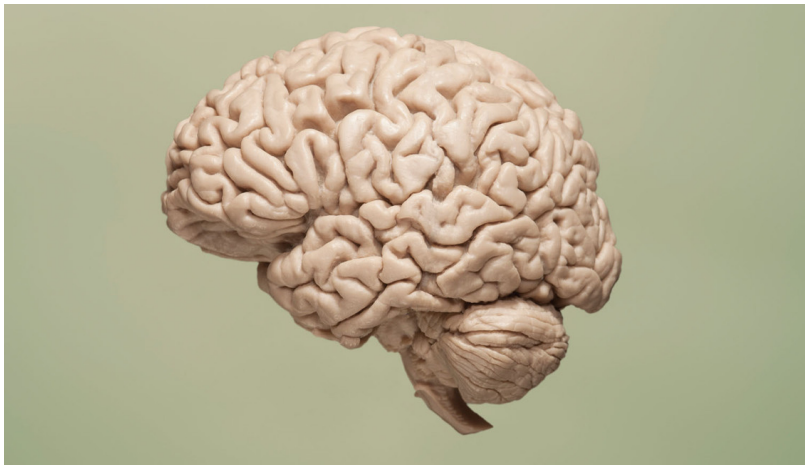
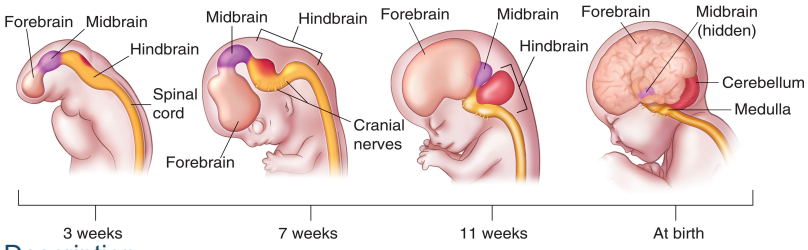


Figure 3.2 View of a Human Brain.

Chris Parsons / DigitalVision / Getty Images



Description

Figure 3.3 The Brain Develops From a Tubular Structure.

The Forebrain

The major structures of the forebrain are the two cerebral hemispheres, the thalamus, and the hypothalamus. The outer layer of the hemispheres, the cortex, is where the highest-level processing occurs in the brain.

The Cerebral Hemispheres

The large, wrinkled **cerebral hemispheres** dominate the brain's appearance (Figure 3.4). They not only are large in relation to the rest of the brain but also are disproportionately larger in humans than in other primates (Deacon, 1990). The **longitudinal fissure** that runs the length of the brain separates the two cerebral hemispheres, which are nearly mirror images of each other in appearance. Often the same area in each hemisphere has identical functions as well, but you will see in later chapters that this is not always the case. The simplest form of *asymmetry* is that each hemisphere receives most of its sensory input from the *opposite* side of the body (or

of the world, in the case of hearing and vision) and provides most of the control of the opposite side of the body.

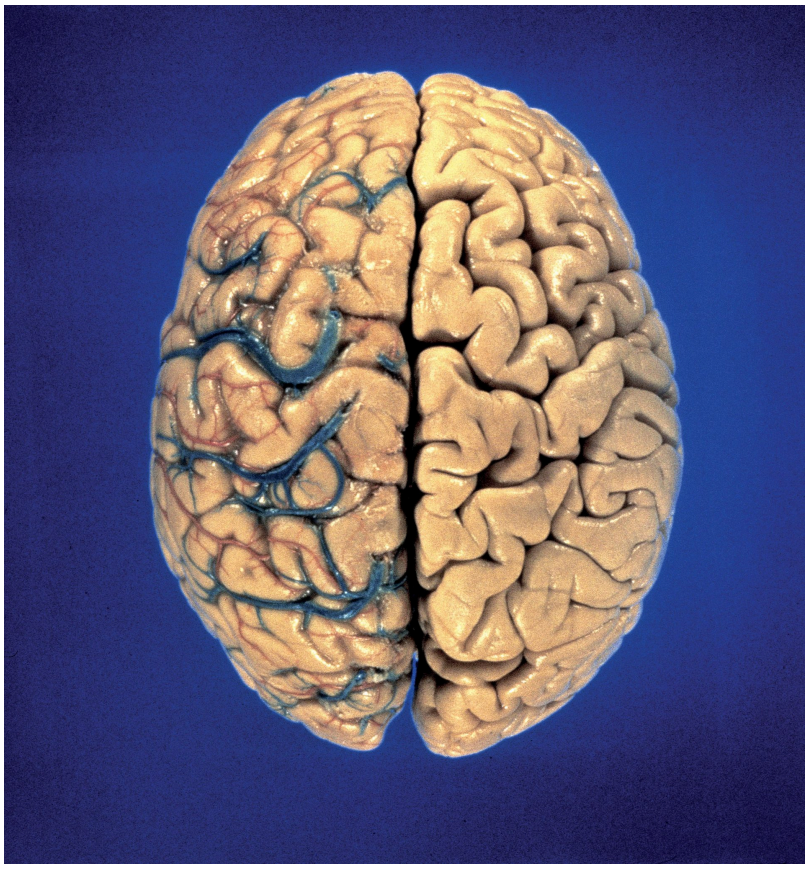
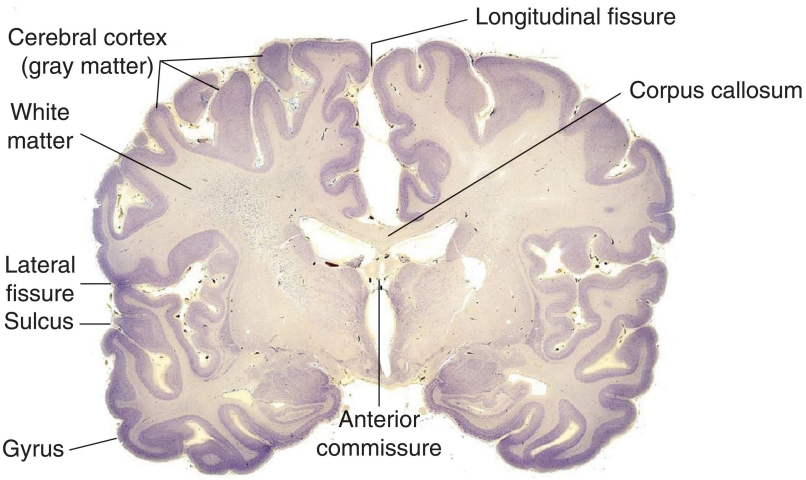


Figure 3.4 Human Brain Viewed From Above.
This photo shows the cerebral hemispheres and longitudinal fissure. The blood vessels have been removed from the right hemisphere.

© David Bassett/Science Source.

Look again at Figures 3.2 and 3.4. The brain's surface has many ridges and grooves that give it a very wrinkled appearance; the term we use is *convoluted*. Each ridge is called a **gyrus** ; the groove or space between two gyri is called a **sulcus** or, if it is large, a **fissure**. You can see how the gyri are structured in the cross section of a brain in Figure 3.5. The outer surface is the **cortex** (literally, "bark"), which is made up mostly of the cell bodies of neurons; because cell bodies lack myelin, the cortex looks grayish in color, which is why it is referred to as gray matter. Remember that neural processing occurs where neurons synapse onto other neurons, which indicates why the cortex is so important. The cortex is only 1.5 to 4 millimeters (mm) thick, but the convolutions increase the amount of cortex by tripling the surface area. The convolutions also provide the axons with easier access to the cell bodies than if the developing cortex thickened instead of wrinkling. The axons come together in the central core of each gyrus, where their myelination gives the area a whitish appearance. Notice how the white matter of each gyrus joins with the white matter of the next gyrus, creating the large bands of axons that serve as communication routes, both within each hemisphere and between the two hemispheres.



Description

Figure 3.5 Section of Human Brain Showing Gyri and Sulci.

Source: Reproduced with permission from http://www.brains.rad.msu.edu, and http://brainmuseum.org, supported by the U.S. National Science Foundation.

? Why is a wrinkled brain better than a smooth one?

You've overslept, and now you find yourself running to your early morning test, fretting about being late while rehearsing answers to the questions you expect on the exam. You interrupt your thoughts only when you have to dodge a bicyclist; your heart rate increases even further with your anger at the student for riding on the sidewalk. Do you ever wonder how your brain pulls all this off?

It will take the rest of this text to *start* answering that question, but this is a good time to mention two ways the brain's organization helps it be more efficient. First, the cortex in humans and most mammals is arranged in layers; the number of layers is usually six, though a particular layer may be absent in some areas. The layers stand out from each other because they are separated by fibers that serve the cell bodies, but they also differ in appearance: They vary in type and size of cells and in the concentration of cell bodies versus axons (see Figure 3.6a). There are differences in function as well. Some researchers have concluded that Layer I is inhibitory, II and III are associational, IV is sensory, and V and VI have motor functions (Buxhoeveden & Casanova, 2002; Larkum, 2013).

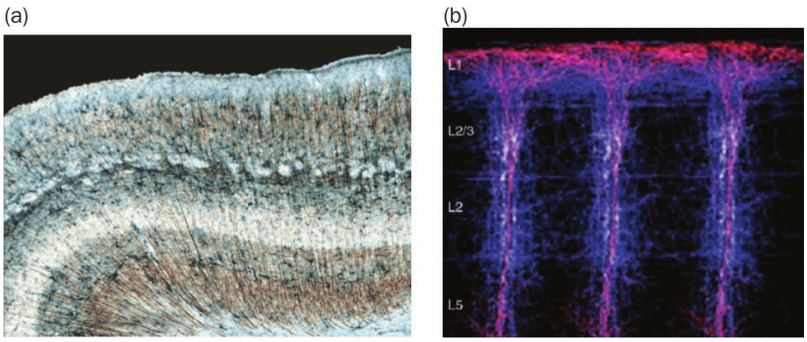


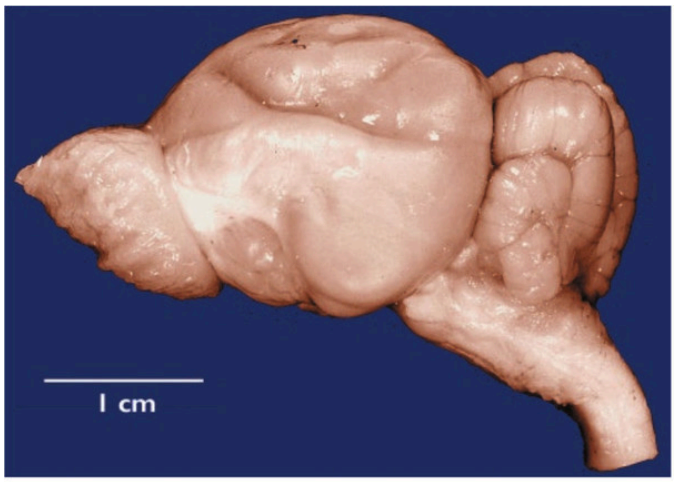
Figure 3.6 Layers and Columns of the Cortex.
(a) Photograph of a section of the cortex, revealing its layered organization. (b) Photograph showing the columnar arrangement of cells in the cortex; the numbers on the left identify the cortical layers.

Source: (a) “Human-Specific Organization of Primary Visual Cortex: Alternating Compartments of Dense Cat-301 and Calbindin Immunoreactivity in Layer 4A,” by Todd M. Preuss and Ghislaine Q. Coleman, *Cerebral Cortex, 12*(7), pp. 671–691, doi:10.1093/cercor/12.7.671. (b) Reconstructed neurons from the Blue Brain Project © BBP/EPFL.

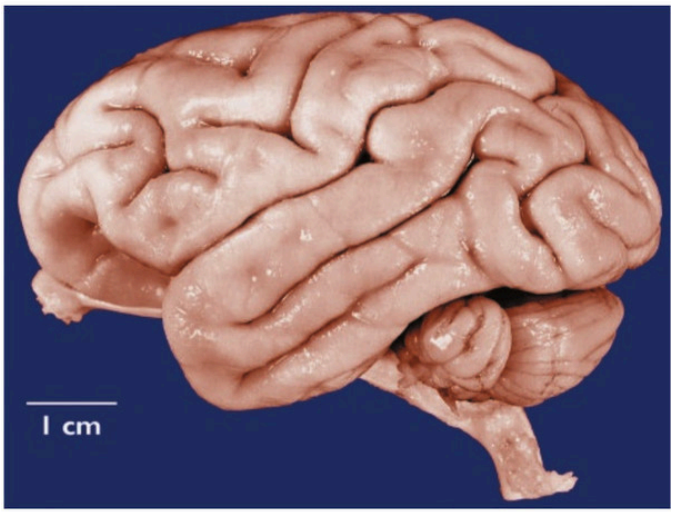
Second, the cells of the cortex are organized into groups of 80 to 100 interconnected neurons, which are arranged in columns running perpendicular to the cortical surface (Figure 3.6b; Buxhoeveden & Casanova, 2002). They provide a vertical unification of the cortex’s horizontal layers, which contributes to their role as the primary information-processing unit in the cortex (Torii, Hashimoto-Torii, Levitt, & Rakic, 2009). The cells in a column have a similar function; for example, they may receive input from the same area on the skin’s surface, while surrounding columns serve adjacent locations. In the visual cortex, the cells in a column may detect object edges at a particular orientation, while surrounding columns respond to edges at a slightly different orientation. Having similar functions grouped close together in well-connected columns helps the brain work quickly and efficiently.

Students often ask whether intelligent people have bigger brains. Bischoff, the leading European anatomist in the 19th century, argued that the greater average weight of men’s brains was infallible proof of their intellectual superiority over women. When he died, his brain was removed and added to his extensive collection, as his will had specified; ironically, it weighed only 1,245 grams (g), less than the average of about 1,250 g for women (“Proof?” 1942). There actually is a tendency for people with larger brains to be more intelligent (Willerman, Schultz, Rutledge, & Bigler, 1991), but the relationship is small and highly variable. What this means is that factors other than brain size are more important; otherwise, women would be less intelligent than men, as Bischoff claimed, but we know from research that this is not the case. When we look at brain size more closely in Chapter 13, you will learn that Einstein’s brain was even smaller than Bischoff’s.

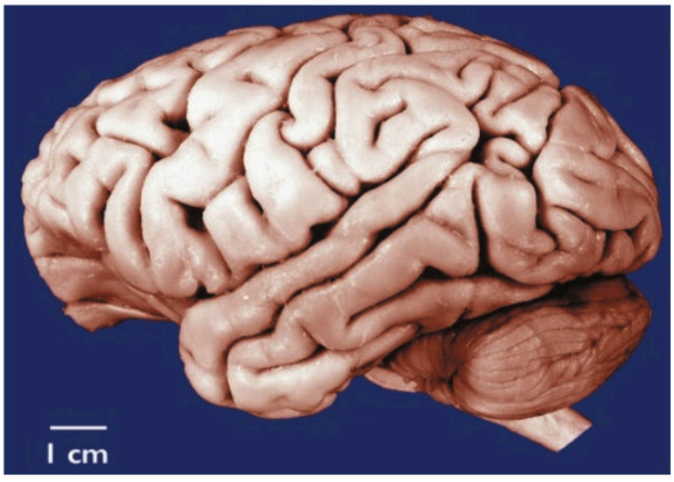
When we look across species, brain size is more related to body size than to intelligence; the brains of elephants and sperm whales are five to six times larger than ours. It is a brain’s complexity, not its size, that determines its intellectual power. Look at the brains in Figure 3.7, and then compare them with the human brain in Figure 3.2. You can see two features that distinguish more complex, more highly evolved brains from less complex ones. One is that the higher brains have more gyri, which means more surface area and, therefore, more cortex. The other is that the cerebral hemispheres are larger in proportion to the rest of the brain. It is no accident that the cerebral hemispheres are perched atop the rest of the brain and the spinal cord. The CNS is arranged in a *hierarchy*; as you ascend from the spinal cord through the hindbrain and midbrain to the forebrain, the neural structures become more complex, and so do the behaviors they control.



(a) Armadillo brain.



(b) Monkey brain.



(c) Chimpanzee brain

(c) Chimpanzee brain.

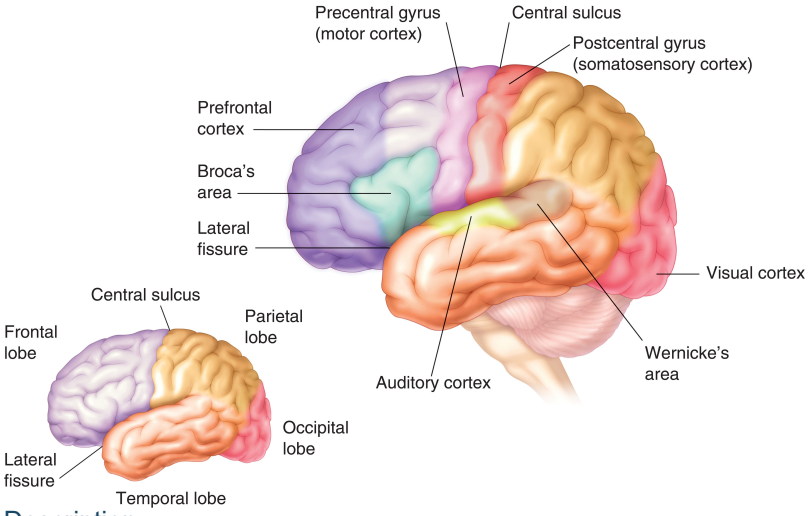
Description

Figure 3.7 Brains of Three Different Mammals.

Source: Reproduced with permission from http://www.brains.rad.msu.edu, and http://brainmuseum.org, supported by the U.S. National Science Foundation.

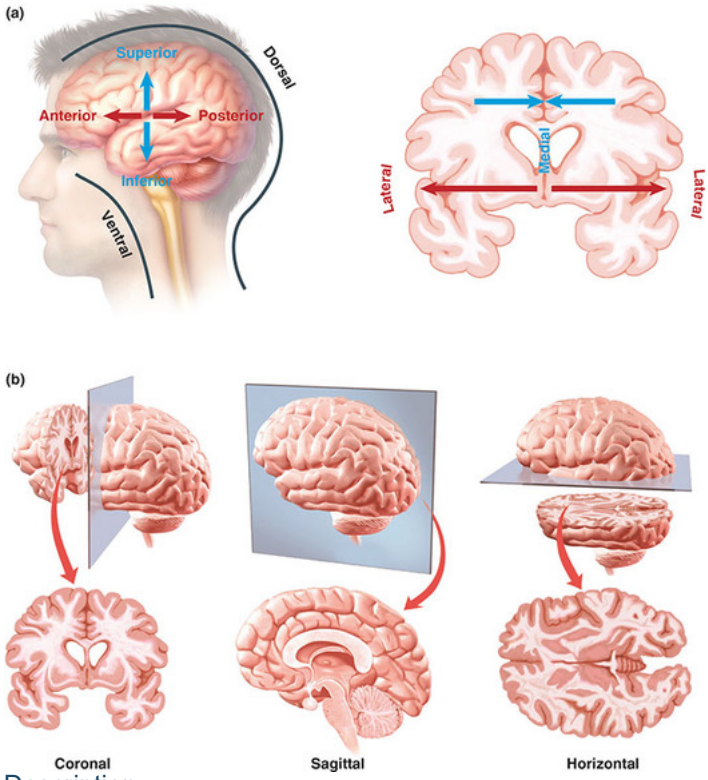
The Four Lobes

The hemispheres are divided into four lobes—frontal, parietal, occipital, and temporal—each named after the skull bone covering it. The lobes are illustrated in Figure 3.8, along with the major functions located within them. These divisions are somewhat arbitrary, but they are very useful for locating structures and functions, so we will organize our discussion around them. Sometimes we need additional precision in locating structures, so you should get used to seeing the standard terms that are used; the most important ones are illustrated in Figure 3.9a. Also, throughout this text, you will see illustrations of the nervous system from a variety of perspectives; until you get more comfortable with the structure of the nervous system, it may be difficult to tell what you are seeing. The images in Figure 3.9b will serve as a guide for understanding the orientation of most of these illustrations.



Description

Figure 3.8 Lobes and Functional Areas on the Surface of the Hemispheres.



Description

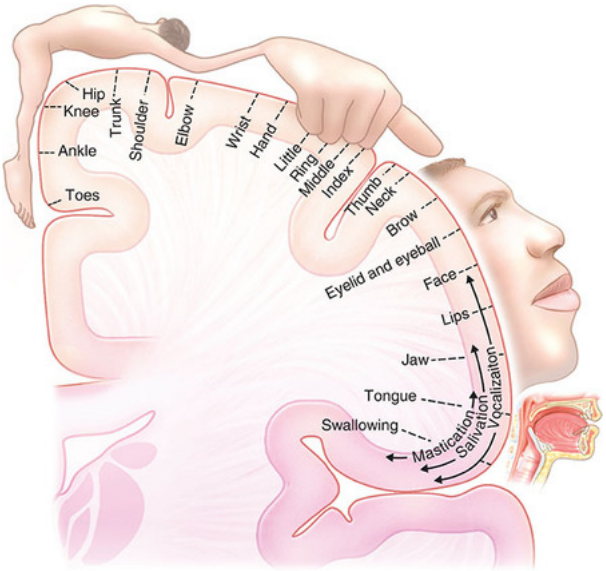
Figure 3.9 Terms Used to Indicate Direction and Orientation in the Nervous System. (a) **Dorsal** means toward the back, and **ventral** means toward the stomach. (This terminology was developed with other animals and becomes more meaningful when you imagine the human on all fours, face forward. **Anterior** means toward the front, and **posterior** means toward the rear. **Superior** is a location above another structure, and **inferior** means below another structure. **Lateral** means toward the side; **medial** indicates toward the middle.
(b) The *coronal plane* divides the brain vertically from side to side, the *sagittal plane* divides it vertically in an anterior-posterior direction, and the *horizontal* plan divides it between the top and bottom. We use these terms when we refer to an image (e.g., a sagittal view) or when the brain is cut along one of these planes (e.g., a horizontal section).

The **frontal lobe** is the area anterior to (in front of) the **central sulcus** and superior to (above) the **lateral fissure**. The functions here are complex and include some of the highest human capabilities. A considerable portion of the frontal lobes is also involved with the control of movement. And because the primary motor area is located along the posterior (rear) boundary of the frontal lobe, we start our discussion there. (You should continue to refer to Figure 3.8.)

? What functions are found in the frontal lobes?

The **precentral gyrus**, which extends the length of the central sulcus, is the location of the primary **motor cortex**, which controls voluntary (nonreflexive) movement. The motor area in one hemisphere controls the opposite side of the body, though it does exert a lesser control over the same side of the body. The parts of the body are “mapped onto” the motor area of each hemisphere in the form of a *homunculus*, which means “little man.” All this means is that the cells that control the muscles of the hand are adjacent to the cells controlling the muscles of the arm, which are next to those controlling the shoulder, and so on (Figure 3.10). The homunculus is distorted in shape, however; the parts of the body that make precise movements, such as the hands and fingers, have proportionally more cortex devoted to their control. The *primary motor cortex*, like other functional areas of the brain,

carries out its work in concert with adjacent *secondary* areas. The secondary motor areas are located just anterior to the primary area. Subcortical (below the cortex) structures, such as the basal ganglia, also contribute to motor behavior. We will talk more about motor control in Chapter 11.



Description

Figure 3.10 The Motor Cortex.
This view shows a cross section (coronal) of the precentral gyrus. The distorted body proportions and facial features of the homunculus indicate the relative amount of motor cortex devoted to those body areas.

Source: Adapted from W. Penfield and T. Rasmussen, The Cerebral Cortex of Man: A Clinical Study of Localization of Function. © 1950 Gale, a part of Cengage Learning, Inc.

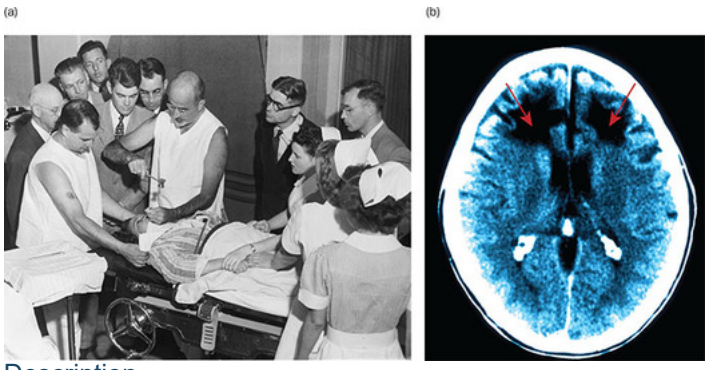
Looking back at Figure 3.8, locate Broca's area anterior to the motor area and along the lateral fissure. **Broca's area** controls speech production, contributing grammatical structure and the motor control involved in speech (via the motor cortex). A patient with damage to this area was asked about a dental appointment; he replied, haltingly, "Yes … Monday … Dad and Dick … Wednesday 9 o'clock … 10 o'clock … doctors … and … teeth" (Geschwind, 1979). Similar problems occur in reading and writing. In another example of hemispheric asymmetry, language activity is controlled mostly by the left hemisphere in 9 out of 10 people. More information about the neural basis of language control will be found in Chapter 9.

The more anterior part of the frontal lobes—the prefrontal cortex in Figure 3.8—is functionally complex. It is the largest region in the human brain, twice as large as in chimpanzees, and it accounts for 29% of the total cortex (Andreasen et al., 1992; Deacon, 1990). The **prefrontal cortex** is involved in planning and organization of behavior, decision making, adjusting behavior in response to its consequences, and planning how to achieve goals (Bechara, Damasio, Tranel, & Damasio, 1997; Fuster, 1989; E. K. Miller & Cohen, 2001). Symptoms of impairment are varied, depending on which part of the prefrontal area is affected (Mesulam, 1986), but malfunction often strikes at the capabilities we consider most human. Schizophrenia and depression, for example, involve dysfunction in the prefrontal cortex.

People with prefrontal damage often engage in behavior that normal individuals readily recognize will get them into trouble. In clinical interviews, they show good understanding of social and moral standards and the consequences of behavior—for example, they can describe several valid ways to develop a friendship, maintain a romantic relationship, or resolve an occupational difficulty—but they are unable to wisely choose among the options. In real life, they suffer loss of friends, financial disaster, and divorce (A. Damasio, 1994). Research indicates that prefrontal damage

impairs the ability to learn from reward and punishment and to control impulses (Bechara et al., 1997). In addition, those with prefrontal damage have reduced behavioral flexibility with respect to choosing possible actions based on a particular situation (Ragozzino, 2007).

Despite the effects of frontal lobe damage, during the 1940s and 1950s, surgeons performed tens of thousands of *lobotomies*, a surgical procedure that disconnects the prefrontal area from the rest of the brain. Initially, lobotomies were performed only on patients with severe schizophrenia, but many overly enthusiastic doctors lobotomized patients with much milder problems. Walter Freeman, shown in Figure 3.11, did more than his share of the 40,000 lobotomies performed in the United States and zealously trained other psychiatrists in the technique (Valenstein, 1986). The surgery calmed agitated patients, but the benefits came at a high price; the patients often became emotionally blunted, distractible, and childlike in behavior. In a follow-up study of patient outcomes, 49% were still hospitalized, and less than a fourth of the others were living independently (A. Miller, 1967). Lack of success with lobotomy and the introduction of psychiatric drugs in the 1950s made the surgery a rare therapeutic choice. Now **psychosurgery**, the use of surgical intervention to treat cognitive and emotional disorders, is generally held in disfavor, unlike brain surgery to treat problems such as tumors. A Further Look describes the most famous case of accidental lobotomy.



Description

Figure 3.11 Lobotomy Procedure and a Lobotomized Brain.
(a) Walter Freeman inserts his instrument between the eyelid and the eyeball, drives it through the skull with a mallet, and moves it back and forth to sever the connections between the prefrontal area and the rest of the brain. (b) A horizontal view of a brain shows the gaps (arrows) produced by a lobotomy.

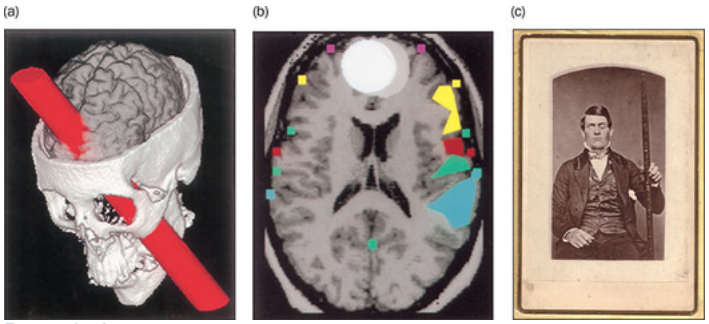
Source: (a) © Living Art Enterprises, LLC/Science Source. (b) © Living Art Enterprises, LLC/Science Source.

A Further Look:

The Case of Phineas Gage

In 1848, Phineas Gage, a 25-year-old railroad construction foreman in Cavendish, Vermont, was tamping explosive powder into a blasting hole when the charge ignited prematurely and drove the 3.5-foot-long (1.15-m) tamping iron through his left cheek and out the top of his skull. Gage not only regained consciousness immediately and was able to talk and to walk with the aid of his men but also survived the accident with no impairment of speech, motor abilities, learning, memory, or intelligence. However, his personality was changed dramatically. He became irreverent and profane, and although Gage previously was the most capable man employed by the railroad, he no longer was dependable and had to be dismissed. He wandered about for a dozen years doing manual labor, never able to live fully independently, and died in the care of his family following seizures that apparently resulted from the injury.

Almost a century and a half later, Hanna Damasio and her colleagues carried out a belated postmortem examination of Gage's skull (H. Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994). Combining measurements from the skull with a three-dimensional computer rendering of a human brain, they reconstructed the path of the tamping iron through Gage's brain (see the accompanying figure). They concluded that the accident damaged frontal lobe areas that are involved in processing emotion and making rational decisions in personal and social matters. More recently, Jack Van Horn and colleagues at UCLA extended Damasio's work by calculating how much the white matter pathways—the myelinated axons that create the circuitry of the brain—would have been damaged by Gage's accident (Van Horn et al., 2012). By simulating the injury using averaged scans of healthy men's brains, they calculated that damage was limited to about 4% of the cerebral cortex and limited to the left hemisphere but that the white matter pathways suffered greater damage, with more than 10% of the connections to other parts of the brain disrupted. At the time of Gage's accident, physiologists were debating whether different parts of the brain have specific functions or are equally competent in carrying out functions. Gage's experience had such an important influence in tipping the balance toward localization of function that in 1998 scientists from around the world gathered in Cavendish to commemorate the 150th anniversary of the event (G. Vogel, 1998).



Description

(a) Gage's skull. (b) A rendering of Gage's skull, showing the likely path of the rod and the white matter pathways damaged. (c) Phineas Gage, with the tamping iron.

Sources: (a) and (b) Reprinted with permission from J. D. Van Horn et al., "Mapping Connectivity Damage in the Case of Phineas Gage," *PLoS ONE, 7,* e37454. © 2012. Reprinted by permission from PLoS ONE. (c) Public domain.

The **parietal lobes** are located superior to the lateral fissure and between the central sulcus and the occipital lobe. The **primary somatosensory cortex**, located on the postcentral gyrus, processes the skin senses (touch, warmth, cold, and pain) and the senses that inform us about body position and movement (see Figure 3.8 again). Like the motor cortex, the somatosensory area serves primarily the opposite side of the body. The somatosensory cortex also is organized as a homunculus, but in this case, the size of each area depends on the sensitivity in that part of the body. When we discuss the senses of vision and hearing in later chapters, you will learn that this mapping is a general principle of brain organization. Also, this is a good place to point out that the sensory areas of the brain are often referred to as *projection areas*, as in *somatosensory projection area*.

? What functions are found in the parietal lobes?

Each of the lobes contains **association areas**, which carry out further processing beyond what the primary area does, often combining information from other senses. Parietal lobe association areas, for example, receive input from the body senses and from vision; they help the person identify objects by touch, determine the location of the limbs, and locate objects in space. Damage to the posterior parietal cortex may produce **neglect**, a disorder in which the person ignores objects, people, and activity on the side opposite the damage. This occurs much more frequently when the damage is in the right parietal lobe. The person may fail to shave or apply makeup on the left side of the face. In some cases, a stroke patient with a paralyzed arm or leg

will deny that anything is wrong and even claim that the affected limb belongs to someone else.

The lateral fissure separates the temporal lobe from the frontal and parietal lobes. The **temporal lobes** contain the auditory projection area, visual and auditory association areas, an additional language area, and structures important in learning and memory (see Figure 3.8). The **auditory cortex**, which receives sound information from the ears, lies on the superior (uppermost) gyrus of the temporal lobe, mostly hidden from view within the lateral fissure. Just posterior to the auditory cortex is **Wernicke's area**, an association area that interprets language input arriving from the nearby auditory and visual areas; it also generates spoken language through Broca's area and written language by way of the motor cortex. When Wernicke's area is damaged, the person has trouble understanding speech or writing; the person can still speak, but the speech is mostly meaningless. Like Broca's area, this structure is found in the left hemisphere in most people.

? What functions are found in the temporal lobes?

The **inferior temporal cortex**, in the lower part of the lobe, as the name implies, plays a major role in the visual identification of objects. People with damage in this area have difficulty recognizing familiar objects by sight, even though they can give detailed descriptions of the objects. They have no difficulty identifying the same items by touch. They may also fail to recognize the faces of friends and family members, though they can identify people by their voices. The neurologist Oliver Sacks (1990) described a patient who talked to parking meters, thinking they were children. Considering his strange behavior, it seems remarkable that he was unimpaired intellectually. As you read about cases like this one and hear of patients who do things like denying ownership of their paralyzed leg, you may begin to understand that human capabilities are somewhat independent of each other because they depend on different parts of the brain.

When the neurosurgeon Wilder Penfield (1955) stimulated patients' temporal lobes, he often elicited what appeared to be memories of visual and auditory experiences. Penfield was doing surgery to remove malfunctioning tissue that was causing epileptic seizures. Before the surgery, Penfield would stimulate the area with a weak electrical current and observe the effect; this allowed him to distinguish healthy tissue and important functional areas from the diseased tissue he wished to remove (Figure 3.12).

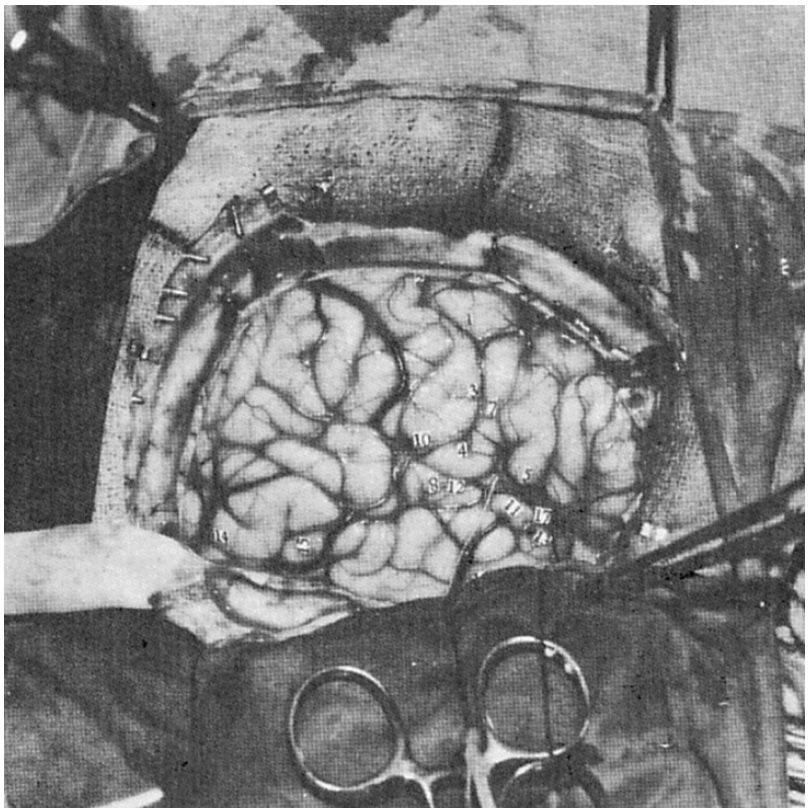


Figure 3.12 Brain of One of Penfield's Patients.
The numbered tags allowed Penfield to relate areas to patients' responses.

Source: From *The Excitable Cortex in Conscious Man*, by Wilder Penfield, 1958. Courtesy of Dennis Coon and Liverpool University Press, Liverpool, UK © 1958. Used with permission.

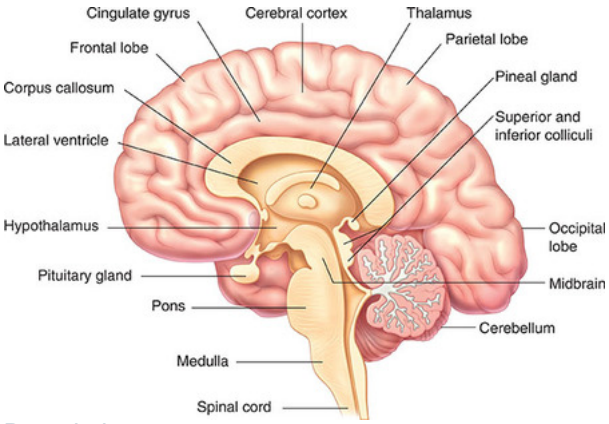
The patients were awake because their verbal report was needed for carrying out this mapping; because brain tissue has no pain receptors, patients required only a local anesthetic for the surgery. Stimulation of primary sensory areas provoked only unorganized, meaningless sensations, such as tingling, lights, or buzzing sounds. But when Penfield stimulated the association areas of the temporal cortex, 25% of the patients reported hearing music or familiar voices or, occasionally, reliving a familiar event. One time, the patient hummed along with the music she was "hearing," and the nurse, recognizing the tune, joined in by supplying the lyrics. (Does this not sound like a scene from a Monty Python movie—a sing-along during brain surgery?) People with epileptic activity or brain damage in their temporal lobes sometimes heard familiar tunes as well. Unfortunately, Penfield made no attempt to verify that the apparent memories were factual rather than a sort of electrically induced dream; we will see in Chapter 12, however, that the temporal lobe's role in memory is significant.

Finally, the **occipital lobes** are the location of the **visual cortex**, which is where visual information is processed (see Figure 3.8). The primary projection area occupies the posterior tip of each lobe; anterior to the primary area are four association areas that detect individual components of a scene, such as color, movement, and form; this information is then combined and processed further in other association areas, particularly in the temporal and parietal lobes. Just as the somatosensory and motor areas are organized to represent the shape of the body, the visual cortex contains a map of visual space because adjacent receptors in the back of the eye send neurons to adjacent cells in the visual cortex.

Now that you are familiar with the four lobes and some of the functions located in the cortex, we will direct our tour to structures below the surface.

The Thalamus and Hypothalamus

Deep within the brain, the **thalamus** lies just below the lateral ventricles, where it receives information from all the sensory systems except olfaction (smell) and relays it to the respective cortical projection areas. (Figure 3.13 is a sagittal view of a brain sliced down the middle to show the structures described in this section.) Many other neurons from the thalamus project more diffusely throughout the cortex and help arouse the cortex when appropriate. There are actually two thalami, a right and a left, lying side by side. We will discuss additional functions for the structure in later chapters.



Description

Figure 3.13 Sagittal View of the Interior Features of the Human Brain.
In this view, the cut has been made between the cerebral hemispheres. Everything above the midbrain is forebrain; everything below is hindbrain.

The **hypothalamus**, a smaller structure just inferior to the thalamus, plays a major role in controlling emotion and motivated behaviors, such as eating, drinking, and sexual activity (see Figure 3.13). The hypothalamus exerts this influence largely through its control of the autonomic nervous system, which we will consider shortly. The hypothalamus also influences the body's hormonal environment through its control over the pituitary gland. In Figure 3.13, the pituitary appears to be hanging down on its stalk just below the hypothalamus. The pituitary is known as the *master gland* because its hormones control other glands in the body. The hypothalamus, which, like the thalamus, is paired, contains perhaps the largest concentration of nuclei important to behavior in the entire brain.

? What functions do the thalamus and hypothalamus perform?

? What functions are found in the occipital lobes?

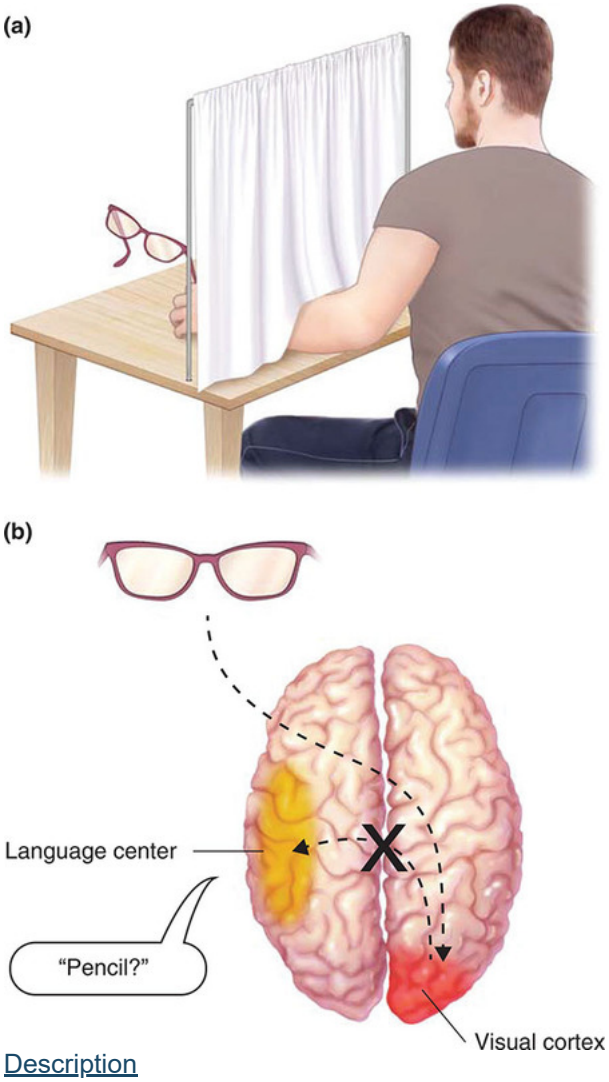
Just posterior to the thalamus is the pineal gland. You can see in Figure 3.13 why it was once called the "third eye" and was Descartes's best candidate for the seat of the soul (see Chapter 1): It is a single, unpaired structure, attached by its flexible stalk just below the hemispheres. In reality, the **pineal gland** secretes melatonin, a hormone that induces sleep; it controls seasonal cycles in nonhuman animals and participates with other structures in controlling daily rhythms in humans.

The Corpus Callosum

If you were to look inside the longitudinal fissure between the two cerebral hemispheres, you would see that the hemispheres are distinctly separate from each other. A couple of inches below the brain's surface, the longitudinal fissure ends in the **corpus callosum**, a dense band of fibers that carry information between the hemispheres. The corpus callosum is visible in Figure 3.13; you can see it from

another perspective, along with a smaller band of crossing fibers, the anterior commissure, by looking back at Figure 3.5. You know that the two hemispheres carry out somewhat different functions, so you can imagine that they must communicate with each other constantly to integrate their activities. In addition, incoming information is often directed to one hemisphere—visual information appearing to one side of your field of view goes to the hemisphere on the opposite side, just as information from one side of your body does. This information is "shared" with the other hemisphere through the crossing fibers, especially the corpus callosum; the car that is too close on your left is registered in your right hemisphere, but if you are steering with your right hand, it is your left hemisphere that must react.

Occasionally, surgeons have to sever the corpus callosum in patients with incapacitating epileptic seizures that cannot be controlled by drugs or other treatments. The surgery prevents the out-of-control neural activity in one hemisphere from engulfing the other hemisphere as well. The patient is then able to maintain consciousness during seizures and to lead a more normal life. These patients have been very useful for studying differences in the functions of the two hemispheres, because a stimulus can be presented to one hemisphere and the information will not be shared with the other hemisphere. Studies of these individuals have helped establish, for example, that the left hemisphere is more specialized for language than the right hemisphere and that the right hemisphere is better at spatial tasks and recognizing faces (Gazzaniga, 1967; Nebes, 1974). An example is shown in Figure 3.14. We will explore this topic further when we discuss consciousness in Chapter 15.



Description

Figure 3.14 A Patient With Severed Corpus Callosum Identifying Objects by Touch. He cannot say what the object is because the right hemisphere, which receives the information from the hand, has been disconnected from the more verbal left hemisphere. Results are similar for visually presented stimuli and sound information.

Carolina Hrejsa/Body Scientific Intl.

The Ventricles

During development, the hollow interior of the nervous system develops into cavities called **ventricles** in the brain and the central canal in the spinal cord. The ventricles are filled with **cerebrospinal fluid**, which carries material from the blood vessels to the CNS and transports waste materials in the other direction. The *lateral ventricles* (Figures 3.13 and 3.15) extend forward deeply into the frontal lobes and in the other direction into the occipital lobes before they curve around into the temporal lobes. Below the lateral ventricles and connected to them is the *third ventricle*; it is located between the two thalami and the two halves of the hypothalamus, which form the ventricle's walls. The *fourth ventricle* is not in the forebrain, so we will locate it later.

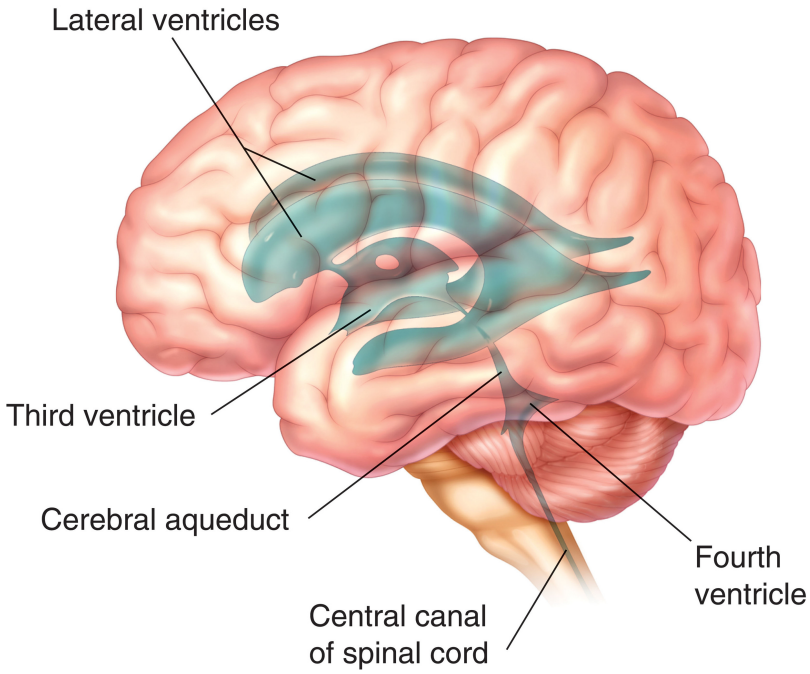


Figure 3.15 The Ventricles of the Brain.

The Midbrain and Hindbrain

The **midbrain** contains structures that have secondary roles in vision, hearing, and movement (Figures 3.13 and 3.16). The **superior colliculi**, for example, help guide eye movements and fixation of gaze, and the **inferior colliculi** help locate the direction of sounds. One of the structures involved in movement is the *substantia nigra*, which projects to the basal ganglia to integrate movements; its dopamine-releasing cells degenerate in Parkinson's disease (see Chapter 11). Another is the *ventral tegmental area*, which plays a role in the rewarding effects of food, sex, drugs, and so on (see Chapter 5). The midbrain also contains part of the reticular formation, which will be described shortly. Passing through the midbrain is the cerebral aqueduct, which connects the third ventricle above with the fourth ventricle below (see Figure 3.15). Notice in Figure 3.16 that the brain takes on a more obvious tubular shape here, reminding us of the CNS's origins. Considering the shape of

these structures and the appearance of the cerebral hemispheres perched on top, you can see why this part of the brain is referred to as the *brain stem*.

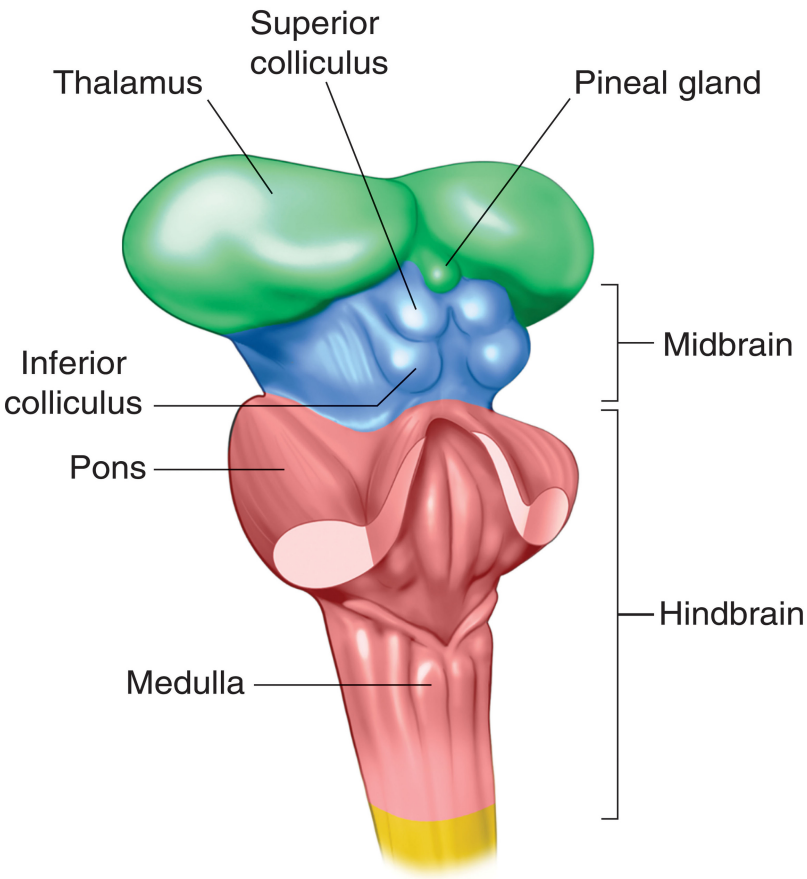


Figure 3.16 The Brain Stem.
The brain stem includes posterior parts of the forebrain (thalamus, hypothalamus, etc.), the midbrain, and the hindbrain. The cerebellum has been removed to reveal the other structures. This is a dorsal view of the brain stem. Refer to Figure 3.13 for its orientation with respect to the entire brain.

The hindbrain is composed of the pons, the medulla, and the cerebellum (see Figures 3.13 and 3.16). The **pons** contains centers related to sleep and arousal, which are part of the reticular formation. The **reticular formation** is a collection of many nuclei running through the middle of the hindbrain and the midbrain; besides its role in sleep and arousal, it contributes to attention and to aspects of motor activity, including reflexes and muscle tone. The word *pons* means “bridge” in Latin, which reflects not only its appearance but also the fact that its fibers connect the two hemispheres of the cerebellum; the pons also has pathways connecting higher areas of the brain with the brain stem. The **medulla** forms the lower part of the hindbrain; its nuclei are involved with control of essential life processes, such as cardiovascular activity and respiration (breathing).

The cerebellum is the second most distinctive-appearing brain structure (see Figures 3.2, 3.8, 3.13, and 3.21). Perched on the back of the brain stem, it is wrinkled and divided down the middle like the cerebral hemispheres—thus its name, which means “little brain.” The most obvious function of the **cerebellum** is refining movements initiated by the motor cortex by controlling their speed, intensity, and direction. A person with cerebellum damage has trouble making precise reaching movements and walks with difficulty because they lose the automatic patterning of movement routines. The cerebellum also plays a role in motor learning, and research implicates it in other cognitive processes, procedural memory, and emotion (Fiez, 1996). With

70% of the brain's neurons in its fist-sized volume, it would be surprising if it did not hold a number of mysteries waiting to be solved.

We have admittedly covered a large number of structures. It may help to see them and their major functions summarized in Table 3.2. But as you review these functions, remember the caveat about localization from Chapter 1 that a behavior is seldom the province of a single brain location but instead results from the interplay of networks of structures.

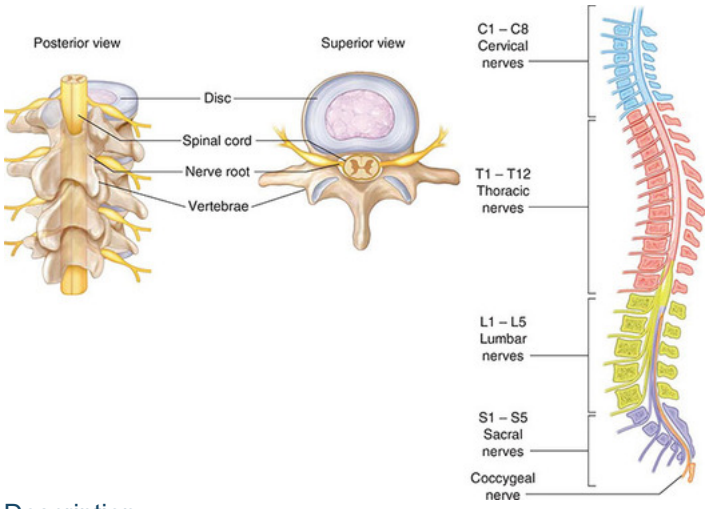
Table 3.2

TABLE 3.2 Major Structures of the Brain and Their Functions.

STRUCTURE	MAJOR FUNCTION
Forebrain	
Frontal lobes	
Motor cortex	Plans and executes voluntary movements
Basal ganglia	Smooths movement generated by motor cortex
Broca's area	Controls speech; adds grammar
Prefrontal cortex	Involved in planning, impulse control
Forebrain	
Parietal lobes	
Somatosensory cortex	Projection area for body senses
Association area	Location of body and objects in space
Temporal lobes	
Auditory cortex	Projection area for auditory information
Wernicke's area	Language area involved with meaning
Inferior temporal cortex	Visual identification of objects
Occipital lobes	
Primary visual cortex	Projection area for visual information
Visual association cortex	Processes components of visual information
Corpus callosum	Communication between the hemispheres
Ventricles	Contain cerebrospinal fluid
Thalamus	Relays sensory information to cortex
Hypothalamus	Coordinates emotional and motivational functions
Pineal gland	Controls daily and seasonal rhythms
Midbrain	
Superior colliculi	Role in vision—for example, eye movements
Inferior colliculi	Role in hearing, such as sound location
Substantia nigra	Integrates movement
Ventral tegmental area	Contributes to rewarding effects of food, sex, and drugs
Hindbrain	
Medulla	Reflexively controls life processes
Pons	Contains centers related to sleep and arousal
Reticular formation	Involved with sleep, arousal, attention, some motor functions
Cerebellum	Controls speed, intensity, direction of movements

The Spinal Cord

The **spinal cord** is a finger-sized cable of neurons that carries commands from the brain to the muscles and organs and sensory information into the brain. Its role is more complicated than that, though. It controls the rapid reflexive response when you withdraw your hand from a hot stove, and it contains pattern generators that help control routine behaviors such as walking. Notice the appearance of the interior of the spinal cord in Figure 3.17; it is arranged just the opposite of the brain, with the white matter on the outside and the gray matter in the interior. The white exterior is made up of myelinated axons—ascending sensory tracts on their way to the brain and descending motor tracts on their way to the muscles and organs.



Description

Figure 3.17 Vertebral Column Anatomy.

Carolina Hrejsa/Body Scientific Intl.

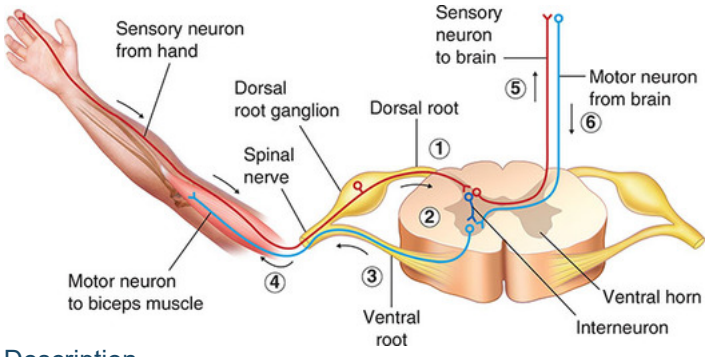
Sensory neurons enter the spinal cord through the **dorsal root** of each spinal nerve. The sensory neurons are unipolar; clustering of their cell bodies in the dorsal root ganglion explains the dorsal root's enlargement. The sensory neuron in Figure 3.17 could be as much as 1 meter (m) long, with its other end out in a fingertip or a toe. The H-shaped structure in the middle of the spinal cord is made up mostly of unmyelinated cell bodies. The cell bodies of motor neurons are located in the *ventral horns*, which is why the ventral horns are enlarged. The axons of the motor neurons pass out of the spinal cord through the **ventral root**. The dorsal root and the ventral root on the same side of the cord join to form a spinal nerve that exits the spine between adjacent vertebrae (the bones that make up the spine).

Each spinal nerve carries information between the central nervous system and specific parts of the body (Figure 3.17). Nerves exiting the seven cervical vertebrae connect the head, neck, shoulders, and elbows. The nerves of the 12 thoracic vertebrae connect to the lower arms and upper torso, as well as the internal organs. The nerves from the five lumbar vertebrae innervate the intestines, legs, and feet. At the bottom, the five vertebrae of the sacrum are fused and target the hips and buttocks, and the tip of the spine (called the coccyx) connects solely to the rectum. Following a spinal injury, any connections between the body and the brain below the location of injury are impaired or lost. And any loss of cartilage between vertebral segments can cause compression of the exiting nerves, resulting in pain and impaired sensation to the body targets of that segment.

? What is the structure of the spinal cord?

Most of the motor neurons receive their input from the brain, either from the motor cortex or from nuclei that control the activity of the internal organs. Notice in Figure 3.18, however, that in some cases, sensory neurons from the dorsal side connect with motor neurons, either directly or through an interneuron. This pathway produces a simple, automatic movement in response to a sensory stimulus; this is called a **reflex**. For example, when you touch a lighted match with your hand, the hot sensory signal travels to the spinal cord, where motor signals are directed out to the muscles of the arm to produce reflexive withdrawal. Many people use the term *reflex* incorrectly to refer to any rapid action a person takes without apparent thought; however, the term is limited to behaviors that are controlled by these direct sensory-motor connections. Besides not requiring thought, reflexive acts occur much more rapidly than the same response produced voluntarily. Reflexes originate in the brain as well as in the spinal cord, and reflexes also affect the internal environment—for example, reducing blood pressure when it goes too high.

Figures Brought to Life



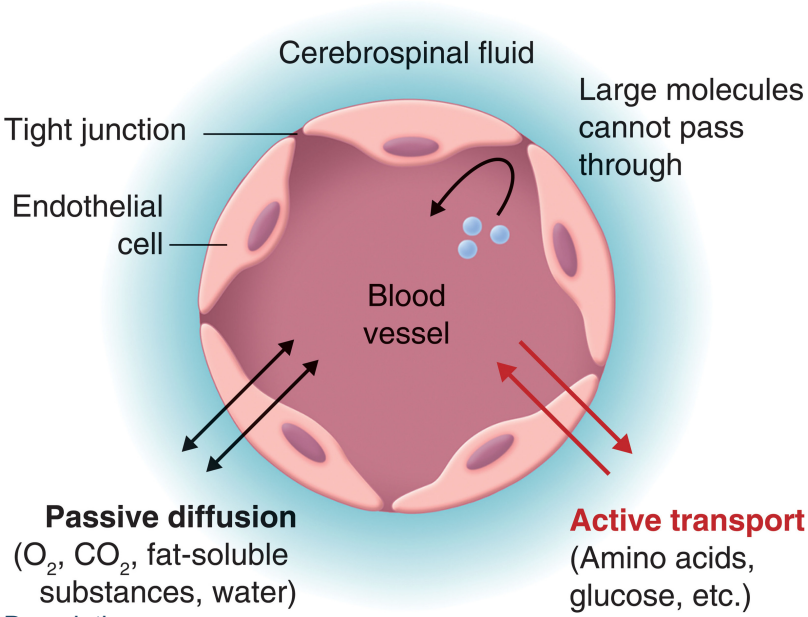
Description

Figure 3.18 Horizontal Cross Section of the Spinal Cord, With Reflex Circuit.
A sensory neuron from the hand transmits signals (1) via the dorsal root of the spinal nerve into the spinal cord, where it (2) forms a reflex arc with a motor neuron that (3) exits through the ventral root and (4) activates the biceps muscle to flex the arm and withdraw the hand. The sensory input also travels (5) up to the brain to produce a sensation. (6) A motor neuron from the brain connects to the motor neuron in the ventral horn; this adds a voluntary activation of the muscle, though more slowly. (In reality, many neurons would be involved.)

Protecting the Central Nervous System

The brain and the spinal cord are delicate organs, vulnerable to damage from blows and jostling, to poisoning by toxins, and to disruption by mislocated or excessive neurotransmitters. Both structures are enclosed in a protective three-layered membrane called the **meninges**. These meninges are the outermost dura layer, the arachnoid layer that separates the blood and the cerebrospinal fluid, and the innermost pia layer. Because the blood is below the tough dura layer, injuries to the head sometimes cause bruising below the dura, resulting in a subdural hematoma (blood-stone). The space between the arachnoid and the CNS is filled with cerebrospinal fluid, which cushions the neural tissue from the trauma of blows and sudden movement. The brain and spinal cord literally float in the cerebrospinal fluid, so the weight of a 1,200- to 1,400-g brain is in effect reduced to less than 100 g. The tough meninges and the cerebrospinal fluid afford the brain some protection from occasional trauma, but the **blood-brain barrier**, which limits passage between the bloodstream and the brain, provides constant protection from toxic substances and from neurotransmitters circulating in the blood, such as norepinephrine, which increases during stress.

Outside the brain, the cells that compose the walls of the capillaries (small blood vessels) have gaps between them that allow most substances to pass rather freely. In the brain, these cells are joined so tightly that easy passage is limited to small molecules, such as carbon dioxide and oxygen, and to substances that can dissolve in the lipid (fat) of the capillary walls (Figure 3.19). Fat solubility accounts for the effectiveness of most drugs, both therapeutic and abused. Most substances needed by the brain are water soluble and cannot pass through on their own, so glucose, iron, amino acids (the building blocks that proteins are made of), and many vitamins must be actively carried through the walls by specialized transporters.



Description

Figure 3.19 The Blood-Brain Barrier.
The tight junctions of the capillary walls prevent passage of large molecules into the brain. Small molecules, such as oxygen and carbon dioxide, pass through freely, as do fat-soluble substances, including most drugs. Water-soluble substances, such as amino acids and glucose, must be transported through the walls.

Not all brain areas are protected by the barrier, however. This is particularly true of brain structures surrounding the ventricles. One of them is the area postrema; when you ingest something toxic, such as an excess of alcohol, the substance passes from the bloodstream into the area postrema. Because the area postrema induces vomiting, your stomach empties quickly—ideally before too much harm is done. This is why the postrema is called the “vomit center” of the brain.

Concept Check

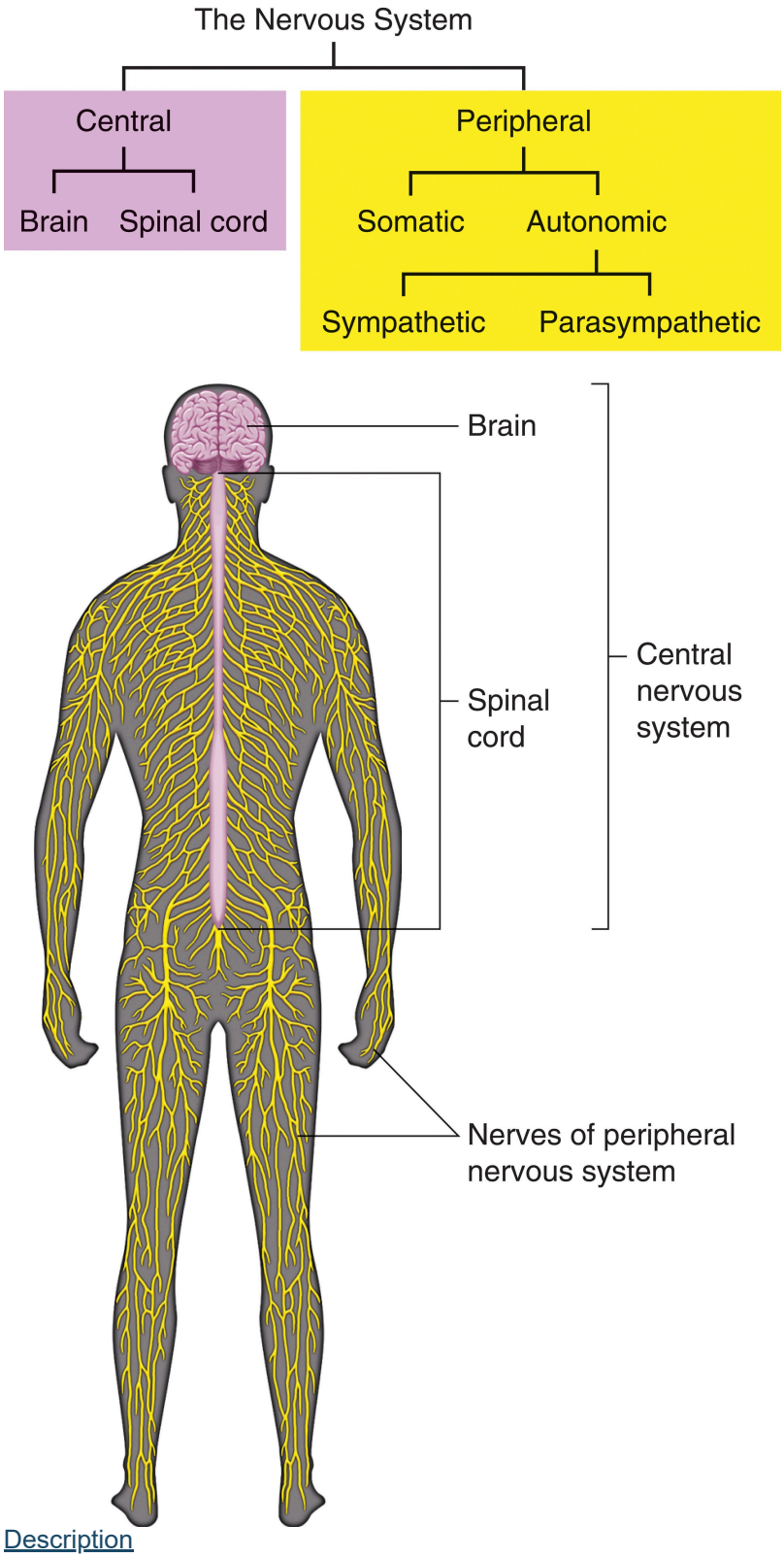
Take a Minute to Check Your Knowledge and Understanding

- What is the advantage of the convoluted structure of the cortex?
- What has been the fate of psychosurgery? What clue from past experience did doctors have that lobotomy in particular might have undesirable consequences?
- Select one of the lobes or the midbrain or the hindbrain and describe the structures and functions located there.
- Describe the pathway of a reflex, identifying the neurons and the parts of the spinal cord involved.

THE PERIPHERAL NERVOUS SYSTEM

The **peripheral nervous system (PNS)** is made up of the **cranial nerves**, which enter and leave the underside of the brain, and the **spinal nerves**, which connect to the sides of the spinal cord at each vertebra. From a functional perspective, the PNS can be divided into the somatic nervous system and the autonomic nervous system. The **somatic nervous system** includes the motor neurons that operate the skeletal

muscles—that is, the ones that move the body—and the sensory neurons that bring information into the CNS from the body and the outside world. The **autonomic nervous system (ANS)** controls smooth muscle (stomach, blood vessels, etc.), the glands, and the heart and other organs. The diagram in Figure 3.20 will help you keep track of these divisions and relate them to the CNS. We dealt with the spinal nerves when we discussed the spinal cord, and we have said all we need to for now about the somatic system, so we will give the rest of our attention to the cranial nerves and the ANS.



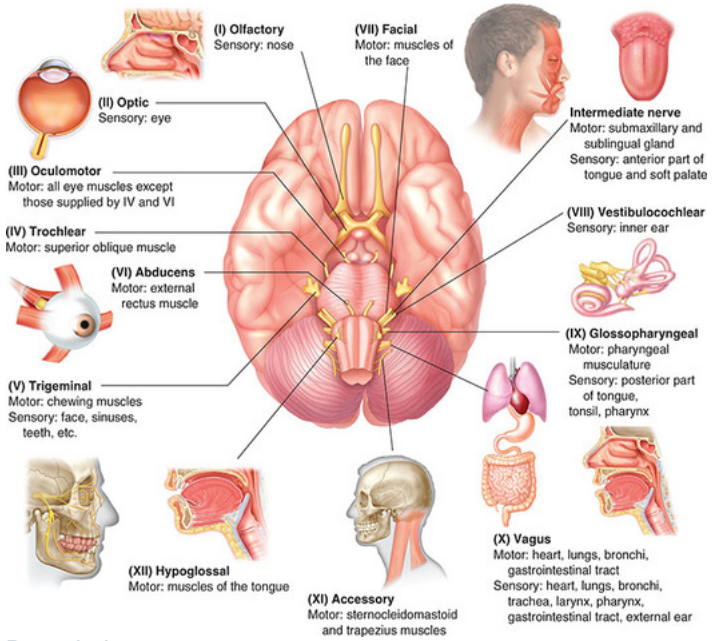
Description

Figure 3.20 Divisions of the Nervous System.

Source: Adapted from *Biological Foundations of Human Behavior*, by J. Wilson, 2003, Belmont, CA: Wadsworth.

The Cranial Nerves

The cranial nerves enter and exit from the ventral side of the brain (Figure 3.21). Whereas the spinal nerves are concerned exclusively with sensory and motor activities within and on the surface of the body, some of the cranial nerves convey sensory information to the brain from the outside world. Two of these, the olfactory nerves and the optic nerves, are often considered part of the brain. One reason for this special status is the brainlike complexity of the olfactory bulb and of the retina at the back of the eye; another is that their receptor cells originate in the brain during development and migrate to their final locations. As a consequence, the olfactory and optic nerves are sometimes referred to as *tracts*.



Description

Figure 3.21 Ventral View of the Brain Showing the Cranial Nerves and Their Major Functions.
Brain landmarks are labeled to help you locate the nerves.

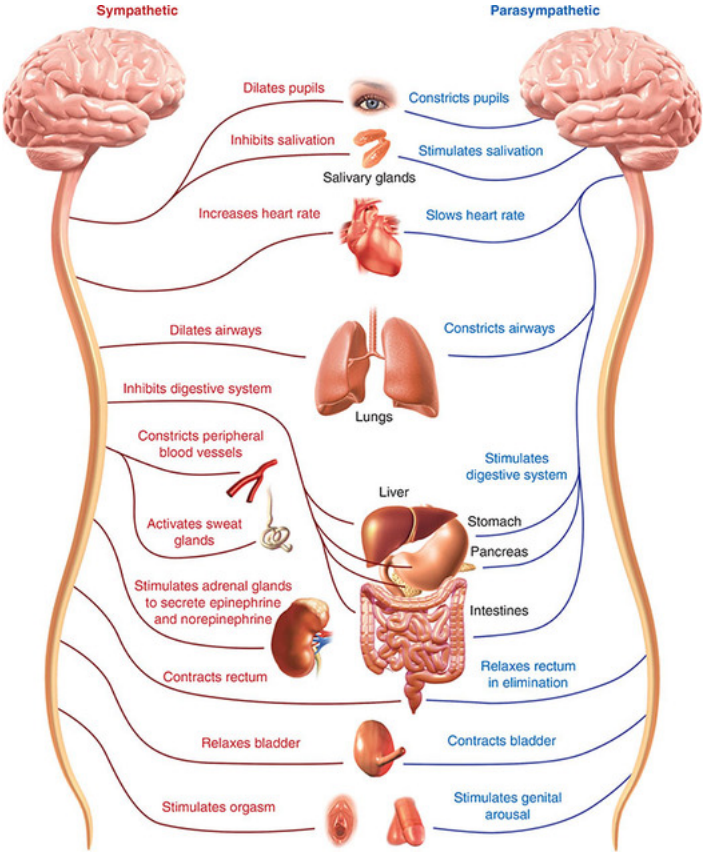
Source: Encyclopaedia Britannica/Contributor/Universal Images Group/Getty.

The Autonomic Nervous System

The functions of the ANS are primarily motor; its sensory pathways provide internal information for regulating its own operations. The ANS is composed of two branches. The **sympathetic nervous system** activates the body in ways that help it cope with demands such as emotional stress and physical emergencies. Your most recent emergency may have been when you overslept on the morning of a big exam. As you raced to class, your heart and breathing sped up to provide your body the resources it needed. Your blood pressure increased as your peripheral blood vessels constricted, shifting blood supply to the internal organs and your brain. Your muscles tensed to help you act, and your sweat glands started releasing sweat to cool your suddenly overheating body. All this activity was just the sympathetic nervous system at work. The **parasympathetic nervous system**, on the other hand, slows the activity of most organs to conserve energy but also activates digestion to renew

energy. These two systems act like a seesaw; when one increases in activity, the other decreases.

The sympathetic branch arises from the middle (thoracic and lumbar) areas of the spinal cord (Figure 3.22; see Figure 3.17 for a refresher). Most sympathetic neurons pass through the **sympathetic ganglion chain**, which runs along each side of the spine; there they synapse with postsynaptic neurons that rejoin the spinal nerve and go out to the muscles and glands they serve. (Others pass directly to ganglia in the body cavity before synapsing.) Because most of the sympathetic ganglia are highly interconnected in the sympathetic ganglion chain, this system tends to respond as a unit. Thus, when you were rushing to your exam, your whole body went into hyperdrive. As you can see in Figure 3.22, the parasympathetic branch rises from the extreme ends of the PNS—in the cranial nerves and in the spinal nerves at the lower (sacral) end of the spinal cord. The parasympathetic ganglia are not interconnected but are located on or near the muscles and glands they control; as a result, the components of the parasympathetic system operate more independently than those of the sympathetic system.



Description

Figure 3.22 The Autonomic Nervous System.
A diagrammatic view of the parasympathetic and sympathetic nerves and their functions. The nerves exit both sides of the brain and spinal cord through the paired cranial and spinal nerves but are shown on one side for simplicity.

? What are the functions of the autonomic nervous system?

Organs are innervated by both branches of the ANS, except for the sweat glands, the adrenal glands, and smooth muscles that constrict blood vessels (these receive only sympathetic activation). It is not accurate to assume that one branch is active at a time and the other completely shuts down. Rather, both are active to some degree

all the time, and the body's general activity reflects the balance between sympathetic and parasympathetic stimulation.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

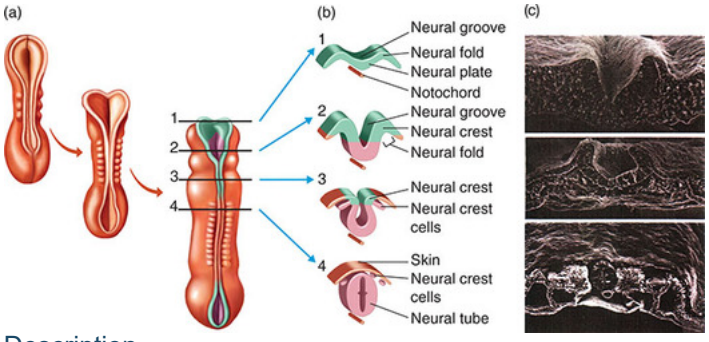
- Which cranial nerves are sometimes referred to as tracts, and why?
- Why does the sympathetic system operate more as a unit than the parasympathetic system does?
- How do the two branches of the ANS interact to regulate internal activity?

DEVELOPMENT AND CHANGE IN THE NERVOUS SYSTEM

Nothing rivals the human brain in complexity, which makes the development of the brain the most remarkable construction project that you or we can imagine. During development, its 100 billion neurons must find their way to destinations throughout the brain and the spinal cord; then they must make precise connections to an average of 1,000 target cells each (Tessier-Lavigne & Goodman, 1996). How this is accomplished is one of the most intriguing mysteries of neurology, but it is a mystery that is being solved a little at a time.

The Stages of Development

You already know that the nervous system begins as a hollow tube that later becomes the brain and the spinal cord. The nervous system begins development when the surface of the embryo forms a neural groove (Figure 3.23). The edges of this groove curl upward until they meet, turning the groove into a neural tube. Development of the nervous system then proceeds in four distinct stages: cell proliferation, migration, circuit formation, and circuit pruning.



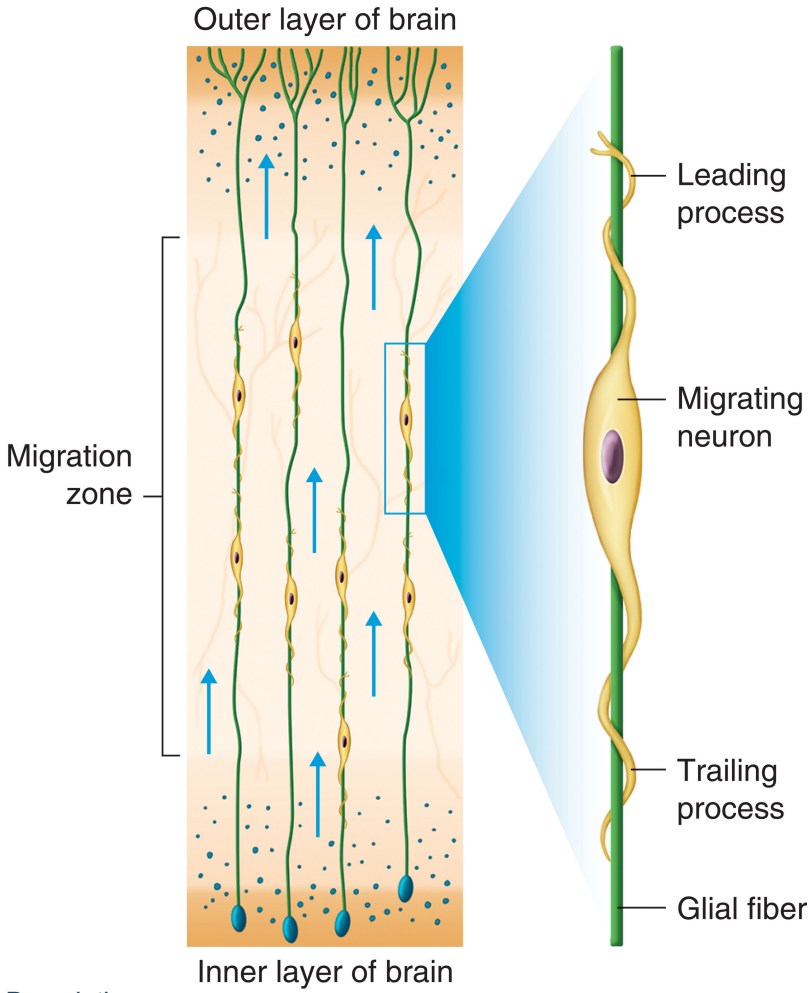
Description

Figure 3.23 Development of the Neural Tube.
The drawings in (a) show how the neural groove closes to form the neural tube, which will then develop into the brain and spinal cord. Details are shown in end views in (b) and in the microscopic photos in (c).

Source: Photos by Kathryn Tosney.

Proliferation and Migration

During **proliferation**, the cells that will become neurons divide and multiply at the rate of 250,000 new cells every minute. Proliferation occurs in the ventricular zone, the area surrounding the hollow tube that will later become the ventricles and the central canal. During **migration**, these newly formed neurons move from the ventricular zone to their final location; most of them move perpendicularly from the ventricular surface using specialized **radial glial cells** (Figure 3.24). An overabundance of neurons migrating into the cortical layers beginning around Week 11 of development causes it to start wrinkling and developing the characteristic sulci and gyri seen in the adult brain. Remember Karen from the beginning of the chapter? This is where development went awry in her brain. The neurons that would have formed her cortex failed to migrate properly and got off their radial glial cell scaffolds too early (J. W. Fox et al., 1998). How neurons move had been unclear until recent efforts (described in A Further Look) revealed a fascinating mechanism.



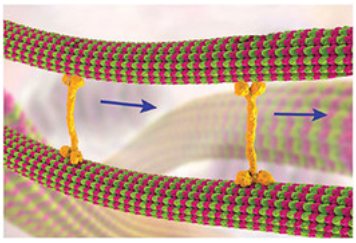
Description

Figure 3.24 A Neuron Migrates Along Glial Scaffolding.
Left: Immature neurons migrate from the inner layer, where they were "born," to their destination between there and the outer layer. Right: A close-up of one of the neurons climbing a radial glial cell scaffold.

Source: Adapted from illustration by Lydia Kibiuk, © 1995.

A Further Look:

Microtubules Move Neurons Along Their Way



Two motor proteins move a microtubule (upper) along a second microtubule.

Source: Adapted with permission from Katerina Kon/Science Photo Library.

Anand Rao and his colleagues thought that the explanation for migrating neurons' ability to move toward their destination lies in their microtubules. Microtubules (MTs) are tubular structures that help maintain the cell's shape and provide a network for transporting molecules through the neuron. This transport is accomplished by motor proteins, which attach themselves at one end to a load, such as a neurotransmitter vesicle, then "walk" the load down the microtubule.

Key to understanding how the developing neurons move is that the motor proteins also can attach themselves to a microtubule as their load and move it along another MT, causing them to slide against each other (W. Lu & Gelfand, 2017). Most MTs are attached to the centrosome, an organelle near the cell's nucleus, but some are unattached. Rao's team was able to show that when attached MTs slide along unattached ones, they tug at the centrosome and tow it—along with the cell body—toward the leading process; this causes the neuron to move forward in inchworm fashion (A. N. Rao et al., 2016). Eventually, most of the MTs detach, so towing of the cell body stops; as the MTs continue sliding against each other, they push against the neuronal membrane to form dendrites and extend the leading process into an axon (W. Lu, Fox, Lakonishokl, Davidson, & Gelfand, 2013; W. Lu & Gelfand, 2017; A. N. Rao et al., 2016).

Different structures form during different stages of fetal development, and the functional role that a neuron will play depends on the time of its "birth" and its location. However, neurons retain considerable flexibility into early infancy. In fact, fetal brain tissue can be transplanted into a different part of an adult brain, and the transplanted neurons will form synapses and assume the function of their new location. This is also true for neural stem cells (intermediate cells that will differentiate into neurons or glia) in the adult brain.

Circuit Formation

? How do neurons find their correct destination?

During **circuit formation**, the axons of developing neurons grow toward their target cells and form functional connections. For example, axons of motor neurons grow toward the spinal cord, and cells in the retina of the eye send their axons to the thalamus, where they form synapses with other neurons. To find their way, axons form **growth cones** at their tip, which sample the environment for directional cues (see Figure 3.25). Chemical and molecular signposts attract or repel the advancing axon, coaxing it along the way (Tessier-Lavigne & Goodman, 1996). By pushing, pulling, and hemming neurons in from the side, the chemical and molecular forces guide the neurons to intermediate stations and past inappropriate targets until they reach their final destinations.

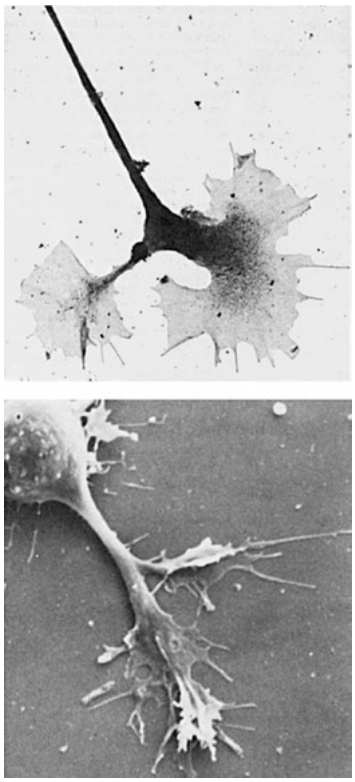


Figure 3.25 Neurons With Growth Cones.

Source: Steven Rothman, MD.

The path to the developing axon's destination is not necessarily direct, but thanks to changing genetic control, it is able to make direction changes along the way. This is most strongly illustrated by an axon whose destination is on the opposite side of the midline. Ordinarily, a migrating axon will grow parallel to the midline without crossing over, because it is repelled by a midline chemical that is under the control of the gene *Robo1*. But at the appropriate location, the gene *Robo3* becomes active; the axon is then attracted to the midline and turns and enters it. At that point, *Robo3* is downregulated; the axon is repelled again and, continuing in the same direction, exits the midline and will not recross (C. G. Woods, 2004).

? What determines which synapses will survive?

Circuit Pruning

The brain produces extra neurons, apparently as a means of compensating for the errors that occur in reaching targets. This overproduction is not trivial: The monkey's visual cortex contains 35% more neurons at the time of birth than in adulthood, and the number of axons crossing the corpus callosum is four times what it will be later in life (LaMantia & Rakic, 1990; R. W. Williams, Ryder, & Rakic, 1987). The next stage of neural development, **circuit pruning**, involves the elimination of excess neurons and synapses. Neurons die if they are unsuccessful in finding a place on a target cell, are crowded off by a more active neuron, or arrive late; the monkey's corpus callosum alone loses 8 million neurons per day during the first 3 weeks after birth.

In a second step of circuit pruning, the nervous system refines its organization and continues to correct errors by eliminating large numbers of excessive synapses. For example, in mature mammals, neurons from the left and right eyes project to alternating columns of cells in the visual cortex, but the connections made during

development are indiscriminate. Synapses are strengthened or weakened depending on whether the presynaptic neuron and the postsynaptic neuron fire together, which increases the acuity of the visual system. Because a single neuron cannot by itself cause another neuron to fire, this is likely to happen when neighboring neurons are also firing and adding summating inputs through overlapping terminals. If a neuron is *not* firing at the same time as its neighbors, it has probably made its connection in the wrong neighborhood. It is thought that the postsynaptic neuron sends feedback to the presynaptic terminals in the form of **neurotrophins**, chemicals that enhance the development and survival of neurons.

In the visual system, sensory stimulation provides neuronal activation that contributes to this refinement. However, pruning of synapses begins in some parts of the visual system even before birth. How can this stimulation occur when visual input is impossible? The answer is that waves of spontaneous neural firing sweep across the fetal retina, providing the activation that selects which synapses will survive and which will not (Hooks & Chen, 2007; Huberman, 2007). In the first few years of the rhesus monkey's life, 40% of the synapses in the primary visual cortex are eliminated, at the stunning rate of 5,000 per second (Bourgeois & Rakic, 1993). This process of producing synapses that will later be eliminated seems wasteful, but targeting neurons' destinations more precisely would require prohibitively complex chemical and molecular codes. Later, the **plasticity** (ability to be modified) of these synapses decreases; a practical example is that recovery from injury to the language areas of the brain is greatly reduced in adulthood. However, the synapses in the cortical association areas are more likely to retain their plasticity, permitting later modification by experience—in other words, learning (Kandel & O'Dell, 1992; W. Singer, 1995).

As impressive as is the brain's ability to organize itself during development, mistakes do occur and for a variety of reasons. Periventricular heterotopia, the problem Karen had (see the beginning of the chapter), is caused by any one of a variety of gene mutations that cause developing neurons to clump near the ventricles rather than migrate to the cortex. **Fetal alcohol syndrome**, which often produces intellectual impairment, is caused by the mother's use of alcohol during a critical period of brain development. The brains of individuals with fetal alcohol syndrome are often small and malformed, and neurons are dislocated (Figure 3.26). During migration, many cortical neurons fail to line up in columns as they normally would because the radial glial cells revert to their more typical glial form prematurely; other neurons continue migrating beyond the usual boundary of the cortex (Clarren, Alvord, Sumi, Streissguth, & Smith, 1978; Gressens, Lammens, Picard, & Evrard, 1992; P. D. Lewis, 1985). Exposure to ionizing radiation, such as that produced by nuclear accidents and atomic blasts, also causes intellectual impairment by interfering with both proliferation and migration. The offspring of women who were in the 8th through 15th weeks of pregnancy during the bombing of Hiroshima and Nagasaki and during the meltdowns at the Chernobyl and Fukushima nuclear generating stations were the most vulnerable, because the rates of proliferation and migration are highest then (Schull, Norton, & Jensh, 1990).

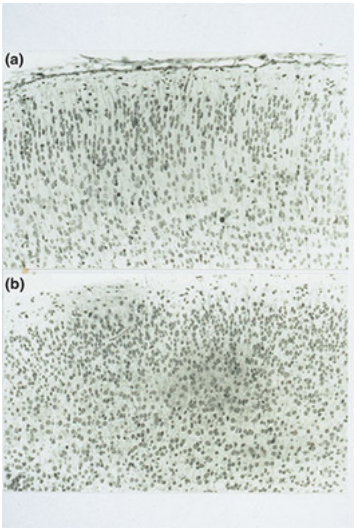


Figure 3.26 Fetal Alcohol Syndrome in the Mouse Brain.
(a) In this cross section of the normal cortex, the neurons (the dark spots) tend to line up in vertical columns. (b) In the alcohol-exposed brain, the neurons are arranged randomly.

Source: From "Ethanol Induced Disturbances of Gliogenesis and Neurogenesis in the Developing Murine Brain: An *in Vitro* and an *in Vivo* Immunohistochemical and Ultrastructural Study," by P. Gressens, M. Lammans, J. J. Picard, and P. Evrard, *Alcohol and Alcoholism, 27,* pp. 219–226. © 1992. Used by permission of Oxford University Press.

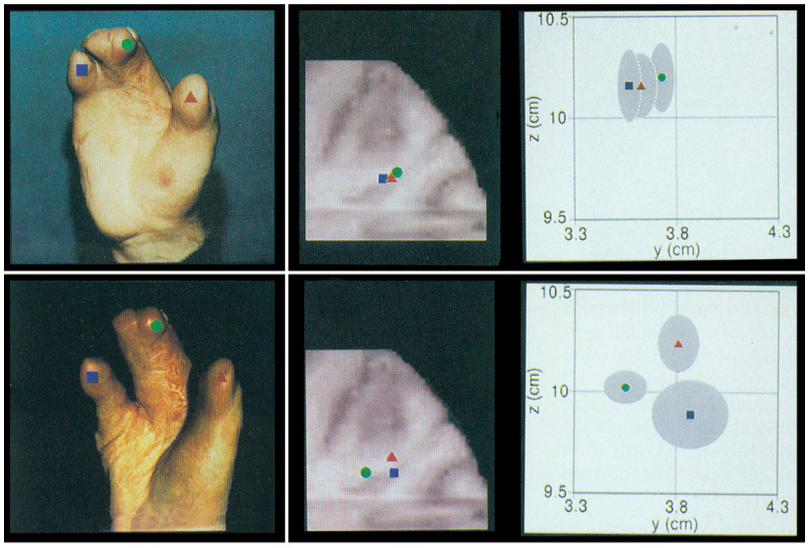
An additional step is required for full maturation of the nervous system: myelination. In the brain, it begins with the lower structures and then proceeds to the cerebral hemispheres, moving from occipital lobes to frontal lobes. Myelination starts around the end of the third trimester of fetal development but is not complete until late adolescence or beyond (Sowell, Thompson, Holmes, Jernigan, & Toga, 1999). There also appears to be a sex difference: During adolescence, males develop slightly greater white matter volume due to larger-diameter axons, while females develop greater white matter density due to more connections (Perrin, Leonard, Perron, Pike, & Pitiot, 2009). This slow process has behavioral implications—for instance, contributing to the improvement through adolescence on cognitive tasks that require the frontal lobes (H. S. Levin et al., 1991). Considering the role of the prefrontal cortex in impulse control and the fact that this area is the last to mature (Sowell et al., 1999), it should come as no surprise that parents are often baffled by their adolescents' behavior.

How Experience Modifies the Nervous System

Stimulation continues to shape synaptic construction and reconstruction throughout the individual's life. For example, training rats to find their way through a maze or just exposing them to a complex living environment causes increased branching of synapses in the cortex (Greenough, 1975). Humans lose neurons as they age, but they develop *more* synapses (Buell & Coleman, 1979), presumably as the result of experience.

Experience-induced change can involve **reorganization**, a shift in connections that changes the function of an area of the brain. For example, in blind people who read Braille, the space in the brain devoted to the index (reading) finger increases, at the expense of the area corresponding to the other fingers on the same hand (Pascual-Leone & Torres, 1993). In a brain scan study, researchers discovered that blind individuals who excel at sound localization had recruited the unused visual area of their brains to aid in the task (Gougoux, Zatorre, Lassonde, Voss, & Lepore, 2005). This rewiring is not random: In blind individuals, trying to locate sounds or touch

activated the area normally involved in visual localization; when cats deaf from birth located objects or detected motion visually, they used areas that ordinarily perform those functions with sounds (Lomber, Meredith, & Kral, 2010; Renier et al., 2010). Much of our brain plasticity is lost after the age of 2 or 3 (Bedny, Konkle, Pelphrey, Saxe, & Pascual-Leone, 2010), but dramatic changes can occur in adulthood. And some of them take place rapidly, as we see in a study of individuals born with a condition called *syndactyly*, in which the fingers are attached to each other by a web of skin. Use of the fingers is severely limited, and the fingers are represented by overlapping areas in the somatosensory cortex. Figure 3.27 shows that after surgery, the representations of the fingers in the cortex became separate and distinct in just 7 days (Mogilner et al., 1993).



Description

Figure 3.27 Changes in the Somatosensory Area Following Surgery for Syndactyly. (a) The hand before (top) and after (bottom) surgery. (b) Images (coronal) showing brain areas responsive to stimulation of the fingers before and after surgery. (c) Graphic representation of the relative size and location of the responsive areas.

Source: From "Somatosensory Cortical Plasticity in Adult Humans Revealed by Magnetoencephalography," by A. Mogilner et al., 1993, *Proceedings of the National Academy of Sciences*, 90, pp. 3593–3597.

? What kinds of changes occur in the brain due to experience?

The 19th-century philosopher and psychologist William James speculated that if a surgeon could switch your optic nerves with your auditory nerves, you would then see thunder and hear lightning (W. James, 1893). James was expressing Johannes Müller's *doctrine of specific nerve energies* from a half century earlier—that each sensory projection area produces its own unique experience regardless of the kind of stimulation it receives. This is why you "see stars" when your skateboard shoots out from under you and the back of your head (where the visual cortex is located) hits the pavement.

But during early development, even this basic principle of brain operation often succumbs to reorganization. In people blind from birth, the visual cortex has nothing to do; as a result, some of the somatosensory pathways take over part of the area, so the visual cortex is activated by touch. But in this case, does the visual cortex produce a visual experience or one of touch? To find out, researchers stimulated the visual cortex of blind individuals by applying an electromagnetic field to the scalp over the occipital area (L. G. Cohen et al., 1997). In sighted people, this disrupted visual performance, but in the blind individuals, the procedure distorted their sense of touch

and interfered with their ability to identify Braille letters. Apparently, their visual area was actually processing information about touch in a meaningful way!

Reorganization does not always produce a beneficial outcome. When kittens were reared in an environment with no visual stimulation except horizontal stripes or vertical stripes, they didn't develop the ability to respond to objects in the other orientation. A cat reared, for example, with vertical stripes would play with a rod held vertically and ignore the rod when it was horizontal. Electrical recording indicated that the cells in the visual cortex that would have responded to horizontally oriented stimuli had reorganized their connections in response to the limited stimulation. In Chapter 11, we will describe one explanation of *phantom pain*, in which people often experience pain that seems to be located in an amputated limb. The pain appears to be due to the intrusion of sensory neurons into the lost limb's somatosensory area (Ortiz-Catalan, 2018).

Damage and Recovery in the Central Nervous System

One reason neuroscientists are interested in the development of the nervous system is because they hope to find clues about how to repair the nervous system when it is damaged by injury, disease, or developmental error. It is difficult to convey the impairment and suffering that result from brain disorders, but the staggering financial costs in Table 3.3 will give you some idea. Here we will focus mostly on stroke and trauma and leave the other sources of injury for later chapters.

A Further Look:

Building a Better Brain

We could make a long list of ways to nurture a healthy brain, but we'll offer just two to illustrate how dietary choices affect our cognitive abilities. The most obvious first place to start is with breastfeeding. In a study of infants born 10 or more weeks early, researchers found that higher breastmilk consumption was related to greater volume of gray matter in the infants' brains at the time of their due date (when they would have been born if they were full term) and, at the age of 7, higher IQ scores, working memory performance, motor abilities, math performance, and intercranial volume (Belfort et al., 2016). Breastmilk also promotes good bacteria in the gut, which not only protect against infections; studies have also found associations between the type of gut bacteria and psychological functions, including stress, anxiety, and cognition (Mayer, Knight, Mazmanian, Cryan, & Tillisch, 2014).

Missed that chance because societal expectations or work demands prevented your mom from breastfeeding? The omega-3 fatty acid docosahexaenoic acid (DHA) is a critical component in neural membranes and is essential for optimal brain health and functioning. Although DHA is readily available in fatty fish, such as salmon, and in fish oil supplements, the average intake of DHA in the United States is less than one third of the recommended level. Dietary DHA intake can speed neural recovery following injury, for example, reducing recovery time from spinal cord injury in animals (Zhou-Hao, Yip, Priestley, & Michael-Titus, 2017) and restoring cognitive function following adolescent traumatic brain injury (Schober et al., 2016). Brain scans of 8- to 10-year-old children while they worked on a sustained attention task showed that those with higher DHA levels had greater functional connectivity, the ability of different areas of the brain to communicate and work with each other (Almeida, Jandacek, Weber, & McNamara, 2016). Importantly, these positive beneficial effects of DHA continue into adulthood. After 12 months on a high-DHA diet, elderly individuals (average age of 88) in nursing homes showed lower levels of depression and less cognitive impairment than the control group (Hashimoto et al., 2016).

Table 3.3

Sources: [1]Olesen, Gustavsson, Svensson, Wittchen, & Jönsson (2011); [2]Eaton et al. (2008); [3]Shirneshan (2013); [4]Gooch, Pracht, & Borenstein (2017); [5]National Institute on Drug Abuse (n.d.).

TABLE 3.3 Annual Costs of Brain Damage and Disorders in the United States.

DAMAGE OR DISORDER	COST (IN BILLION U.S. DOLLARS)	
	United States	30 European Countries[1]
Psychiatric disorders (schizophrenia, mood disorder, anxiety)	340.13[2,3]	355.9
Traumatic brain injury	91.4[4]	41.708
Stroke	116.96[4]	72.38
Alzheimer's disease and other dementias	258.37[4]	132.854
Alcohol and opioid dependency	365.93[5]	84.106
Total	1,172.79	686.948

Sources: [1]Olesen, Gustavsson, Svensson, Wittchen, & Jönsson (2011); [2]Eaton et al. (2008); [3]Shirneshan (2013); [4]Gooch, Pracht, & Borenstein (2017); [5]National Institute on Drug Abuse (n.d.).

Note: Data are corrected for inflation to 2019 values and include direct costs of care and treatment and indirect costs such as crime, lost wages, and financial assistance. Differences between the U.S. and European data are due to a variety of factors, including population size, greater cost of direct health care in the United States, and which indirect costs were included in each study.

Note: Data are corrected for inflation to 2019 values and include direct costs of care and treatment and indirect costs such as crime, lost wages, and financial assistance. Differences between the U.S. and European data are due to a variety of factors, including population size, greater cost of direct health care in the United States, and which indirect costs were included in each study.

Stroke, also known as cerebrovascular accident, is caused by a loss of blood flow in the brain. Most strokes are ischemic, caused by blockage of an artery by a blood clot or other obstruction; hemorrhagic strokes occur when an artery ruptures. The neurons are deprived of oxygen and glucose, of course, but most of the damage is due to *excitotosis* (not to be confused with *exocytosis*, mentioned in Chapter 2). In excitotosis, dying neurons release excess glutamate, which overstimulates the surrounding neurons. The neurons then die as large amounts of calcium enter the cells. Further impairment is caused by edema, an accumulation of fluid that causes increased pressure on the brain. Stroke is the fourth leading cause of death in the United States (Centers for Disease Control and Prevention, 2015a) and a leading cause of long-term disability, including paralysis and loss of language and other functions (Heron et al., 2009). In A Further Look, we discuss a novel treatment for breaking up ischemic clots and treating other problems without invasive surgery.

A Further Look:

Ultrasound Surgery

Source: AP Photo/The Canadian Press, Frank Gunn.

Brain disorders often require surgery, which has its own drawbacks. The use of focused ultrasound is making intervention noninvasive, safer, and more precise. The energy is focused on the target area by an acoustic lens, much the same way as a magnifying glass focuses beams of sunlight. An individual acoustic beam by itself has no effect, but when multiple intersecting beams of ultrasound are focused on a target, they can produce important biological effects. The warming produced can be detected on a brain scan, which allows the surgeon to readjust the location. Targets can be as small as 1 mm^2 or up to 150 mm^2. Increasing the energy level generates enough heat to destroy the target, and the technique can be used to break up blood clots or destroy tumors and other diseased tissue, as well as to silence neural circuits to treat disabling tremors and unbearable pain (Monteith, Gwinn, & Newell, 2015).

Recent work suggests that these techniques can also be applied to neuropsychiatric disorders such as Alzheimer's and Parkinson's diseases, which historically have relied on drugs and invasive treatments (Leinenga, Langton, Nisbet, & Götz, 2016). The therapeutic effects are immediate and without the recovery and side effects typically seen with traditional surgery or radiation treatments. Researchers are also using the technique with transgenic mice that develop the brain pathology and memory deficits characteristic of Alzheimer's disease (Burgess et al., 2014). Their strategy is to activate glial cells and open the blood-brain barrier near memory structures, to allow immune cells to enter the brain and help clear away cellular damage caused by the disease.

Traumatic brain injury (TBI) is caused by an external mechanical force, such as a blow to the head, sudden acceleration or deceleration, or penetration. TBIs account for 30% of all injury deaths and result in more than 55,000 deaths each year in the United States (Centers for Disease Control and Prevention, 2017); about 35% of TBIs are caused by falls, and another 17% result from traffic accidents (Faul, Xu, Wald, & Coronado, 2010). Besides the direct damage to neurons, edema and ischemia (loss of blood supply due to blood clots) take an additional toll. Mild traumatic injury, or concussion as it is more commonly known, is the most common TBI. It results from blows and acceleration-deceleration that occur in automobile accidents, sports activities, and battlefield explosions. Whether or not these traumas are sufficient to cause loss of consciousness, they are often followed by headache, drowsiness, and memory loss, which usually go away if the individual rests for 3 weeks following the injury. Repeated concussions can cause cumulative brain damage. The expression "punch-drunk" refers to dementia pugilistica, the impairment suffered by boxers who didn't know when to quit. However, even a single concussion severe enough to cause brief unconsciousness or amnesia produces brain atrophy detectable 1 year later and correlated with memory and attention deficits (Y. Zhou et al., 2013).

TBI has been very much in the news recently because of its high incidence (up to 3.8 million injuries per year in the United States alone; Faul et al., 2010), especially in sports. A research project at Boston University has found signs of Alzheimer's-like brain disease in autopsies of 87 out of 91 former National Football League (NFL) players (Breslow, 2015a); a suit by thousands of ex-players resulted in a settlement that will cost the NFL upward of $1 billion (Breslow, 2015b). But risk of brain damage isn't limited to professional contact sports. Even heading the ball in women's youth and college soccer can produce impacts 40 to 63 times the force of gravity (Hanlon & Bir, 2012; Lynall et al., 2016), and frequent heading is associated with white matter abnormalities and memory deficits (Lipton et al., 2013).

Limitations on Recovery

Nervous system repair is no problem for some species, particularly amphibians. For example, when Sperry (1943, 1945) severed the optic nerves of frogs, the eyes made functional reconnections to the brain even when the disconnected eye was turned upside down or transplanted into the other eye socket. **Regeneration**, the growth of severed axons, also occurs in mammals, at least in the PNS. So when you fell skateboarding, if you broke your arm so badly that a nerve was severed, the disconnected part of the cut axons would have died, but many of the parts connected to the cell body would have survived and regrown. Myelin provides a guide tube for

the sprouting end of a severed neuron to grow through (W. J. Freed, de Medinaceli, & Wyatt, 1985), and the extending axon is guided to its destination, much as it would be during development (Horner & Gage, 2000).

? What limits central nervous system repair? How might repair be encouraged?

But in the mammalian CNS, damaged neurons encounter a hostile environment. If your skateboarding accident severed neurons in your spinal cord, the axon stumps would sprout new growth, but they would make little progress toward their former target. This is partly because the CNS in adult mammals no longer produces the chemical and molecular conditions that stimulate and guide neuronal growth. In addition, glial cells both produce scar tissue that blocks the original pathway and produce axon growth inhibitors, while immune cells that move into the damaged area possibly interfere with regrowth (D. F. Chen, Schneider, Martinou, & Tonegawa, 1997; Horner & Gage, 2000; Thallmair et al., 1998).

Another way the nervous system could repair itself is by **neurogenesis**, the birth of new neurons. Neurogenesis occurs in several areas of adult animal brains (C. D. Fowler, Liu, & Wang, 2007; Kahn, Hough, Ten Eyck, & Bingman, 2003), but research indicates that it is most extensive in two places. One is the hippocampus, and the other is near the lateral ventricles, supplying the olfactory bulb (Gage, 2000). This research was done by administering bromodeoxyuridine (BrdU), which is taken up in the DNA of cells as they divide; the animals were then sacrificed, and the presence of BrdU in neurons in the brain indicated robust neurogenesis, especially in the hippocampus. In 1998, Peter Eriksson and his colleagues were able to use this technique with deceased cancer patients who had been given BrdU to track the spread of tumors, and they found the first evidence of neurogenesis in the adult human hippocampus. The use of BrdU in humans was banned shortly after that, making replication of the study difficult and leaving other researchers skeptical. Then a team at Stockholm's Karolinska Institute hit on the idea of measuring carbon 14 (C14), which was absorbed by individuals around the world between 1945 and 1963 as a result of above-ground nuclear testing (Spalding et al., 2013). Cellular levels of C14 correspond to atmospheric levels, so the researchers were able to date the birth of new neurons and determine that our hippocampi add 1,400 new neurons every day. While neurogenesis in the human hippocampus is well established, neurogenesis in human olfactory bulbs has been controversial, possibly because it occurs at a much lower rate there (Maheu et al., 2015), and typical tissue processing procedures inadequately preserve the new neurons (Moreno-Jiménez et al., 2019).

These new neurons apparently contribute to the neural plasticity required in learning: Blocking neurogenesis in the hippocampus interferes with certain types of learning that involve that structure, and doing so in the olfactory bulbs impairs learning associations with odors (Lazarini & Lledo, 2011; Ming & Song, 2011). There is no guarantee that this neurogenesis contributes to brain repair following injury. However, neural precursor cells migrate to damaged areas in rat brains following experimentally induced stroke and appear to replace damaged neurons (Parent, 2003). Furthermore, increased neurogenesis has been observed at damage sites in the brains of deceased Alzheimer's patients and Huntington's disease patients (Curtis et al., 2003; Jin et al., 2004). Results such as these suggest that if we could enhance neurogenesis, it might provide a means of self-repair.

Compensation and Reorganization

Although axons do not regenerate and neuron replacement is limited at best, considerable recovery of function can occur in the damaged mammalian CNS. Much of the improvement in function following injury is nonneural in nature and comes about as swelling diminishes and glia remove dead neurons (Bach-y-Rita, 1990). The simplest neural recovery involves **compensation** as uninjured tissue takes over the functions of lost neurons. Presynaptic neurons sprout more terminals to form additional synapses with their targets (Fritschy & Grzanna, 1992; Goodman, Bogdasarian, & Horel, 1973), and postsynaptic neurons add more receptors (Bach-y-Rita, 1990). In addition, normally silent side branches from other neurons in the area become active within minutes of the injury (A. Das & Gilbert, 1995). These synaptic

changes are similar to those occurring during learning; this would explain why physical therapy can be effective in promoting recovery after brain injury.

? What forms of recovery are possible in the human CNS?

A more dramatic form of neural recovery involves reorganization of other brain areas. During recovery of language ability following brain damage or surgery, the functions can be assumed by nearby brain areas or, in the case of massive damage, by the other hemisphere (Guerreiro, Castro-Caldas, & Martins, 1995). Occasionally, an entire hemisphere must be removed because it is diseased. The patients typically do not reach normal levels of performance after the surgery, but they often recover their language and other cognitive skills and motor control to a remarkable degree (Glees, 1980; Ogden, 1989). In these cases, malfunction in the removed hemisphere dated back to infancy, so presumably the reorganization began then, rather than at the time of surgery in late adolescence or early adulthood. In rare instances, people are born entirely lacking a corpus callosum. A further tribute to the brain's plasticity is that 75% of these individuals develop normally, and fewer than 12% are severely impaired (Sotiriadis & Makrydimas, 2012).

Recovery from aphasia (loss of language) and from periventricular heterotopia challenges our understanding of how the brain works. Hydrocephalus provides another such example. **Hydrocephalus** occurs when the circulation of cerebrospinal fluid is blocked and the accumulating fluid interferes with the brain's growth, typically producing severe intellectual impairment. If detected in time, the condition can be treated by installing a drain that shunts the excess fluid into the bloodstream. However, the occasional individual somehow avoids impairment without this treatment. The British neurologist John Lorber described a 26-year-old college student with hydrocephalus whose ventricles were so enlarged that the cerebral walls (between his ventricles and the outer surface of his brain) were less than 1 mm thick, compared with the usual 45 mm (Figure 3.28). Yet he had a superior IQ of 126, had earned an honors degree in mathematics, and was socially normal (Lewin, 1980). It is unclear how these individuals can function normally in the face of such enormous brain deficits. What is clear is that somewhere in this remarkable plasticity lies the key to new revelations about brain function.

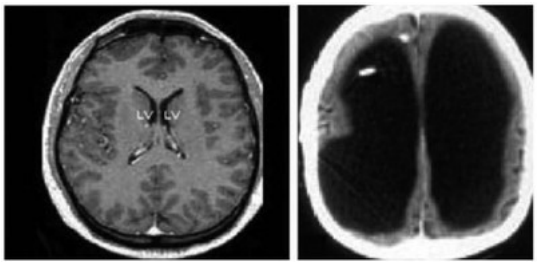


Figure 3.28 Normal Brain and Hydrocephalic Brain.
The ventricles are greatly enlarged and brain tissue is reduced in the brain on the right, compared with the normal brain on the left. The individual has an IQ of 75 (above the cutoff for intellectual impairment), is employed as a civil servant, and has a wife and two children.

Source: Reprinted from "Brain of a White-Collar Worker," by L. Feuillet, H. Dufour, and J. Pelletier, 2007, *The Lancet,* 370, p. 262. © 2007, with permission from Elsevier.

Possibilities for CNS Repair

In 1995, Christopher Reeve, the movie actor best known for his role as Superman, was paralyzed from the neck down when he was thrown from his horse during a competition. Three quarters of his spinal cord was destroyed at the level of the injury (J. W. McDonald et al., 2002). He had no motor control and almost no sensation below the neck; like 90% of similarly injured patients, he experienced little functional

improvement over the next few years. Chicago Bears wide receiver Johnny Knox also suffered a severely damaged spinal cord when a Seattle Seahawks lineman bent him backward almost in half during a game in 2011 (Figure 3.29). Many people thought he would not be able to walk again due to the amount of damage; but unlike Reeve, through intensive treatment by properly trained staff at the time of injury (immobilizing the head and neck, as seen in the figure, and advances in spinal fusion surgery) and during the recovery process, he was able to regain the ability to walk, despite shattering several vertebrae and severely bruising his spinal cord. Although we cannot yet repair severed spinal cords, we have made significant advances in helping injured ones heal.

Figure 3.29 Johnny Knox.

Source: Chicago Tribune/Contributor/Tribune News Service/Getty Images.

In spite of Ramón y Cajal's declaration that there is no regeneration in the CNS, scientists nearly a century later are pursuing several strategies for inducing self-repair following damage like Reeve's and Knox's. These efforts include minimizing the initial damage, encouraging regrowth and new connections, and—the holy grail of stroke and spinal cord treatment—replacing lost neurons. As one example, administering a neuroprotective agent in rats with induced stroke reduced glutamate-induced excitotoxicity, which in turn reduced the area of damage by 40% and minimized the loss of motor functions (Bach et al., 2012). Although the brain releases gamma-aminobutyric acid (GABA) to defend against excitotoxicity, GABA's effect at receptors elsewhere on the neuron is to reduce later plasticity. Researchers at UCLA found a way to block GABA's effect outside the synapse, while leaving its synaptic inhibition intact; as a result, mice treated with the drug recovered 50% more motor function than controls (Clarkson, Huang, MacIsaac, Mody, & Carmichael, 2010).

Several strategies for encouraging axon regrowth are under investigation. One option is to block receptors for the protein Nogo-A, which inhibits regeneration following injury. In monkeys with surgically induced spinal cord damage, a Nogo-A inhibitor produced axon growth across the injured area, and the monkeys recovered 80% of the use of their paralyzed hands (P. Freund et al., 2006; P. Freund et al., 2007). In rats with induced stroke, combining this Nogo-A blocker with inosine doubled the compensatory growth of axon branches into the spinal cord from the intact hemisphere; this restored the rats' skilled reaching to preoperative levels (Zai et al., 2011). In a study with humans, several patients experienced improved motor scores,

and 37% of patients with complete loss of sensation and control below the injury improved (Kucher et al., 2018).

The most graphic axon regrowth results were in a study with rats whose severed spinal cords were treated with electrical stimulation and drugs that increased neural excitability (van den Brand et al., 2012). When the rats were suspended in a sling, circuits in the lower spinal cord enabled them to step in response to a moving treadmill but not to walk voluntarily. But when the electrochemical stimulation was combined with the temptation of a chocolate treat, they were able after 4 to 5 weeks of training not only to walk but to sprint up rat-sized stairs. Compared with untrained rats and rats trained on the treadmill alone, they had an increase in axonal projections around the lesion site that equaled 45% of the original fibers, plus an almost four-fold increase in projections from the cortex to brain-stem motor areas.

The most exciting possibility involves the use of stem cells to replace injured neurons. **Stem cells** are undifferentiated cells that can develop into specialized cells, such as neurons, muscle, or blood cells. Stem cells in the embryo (Figure 3.30) are *pluripotent*, which means that they can differentiate into any cell in the body. The developing cell's fate is determined by chemical signals from its environment that turn on specific genes and silence others. Later in life, adult stem cells lose most of their flexibility, and most are confined to areas with a high demand for cell replacement, such as the skin, the intestine, and bone marrow (the source of blood cells). In the brain, neural stem cells are the source of the neurogenesis we discussed earlier; they are *multipotent*, meaning they can differentiate into any type of neuron as well as glial cells. When embryonic stem cells are placed into an adult nervous system, they tend to differentiate into neurons appropriate to that area; researchers are also learning how to coax adult stem cells to do the same. Results with rats have indicated that stem cells can improve post-injury neural recovery. Two clinical trials with humans were terminated due to lack of improvement, but preclinical studies have suggested that stem cells can differentiate into glial cells and remyelinate neurons, and the results of a clinical trial are expected soon (reviewed in Nori, Ahuja, & Fehlings, 2017).

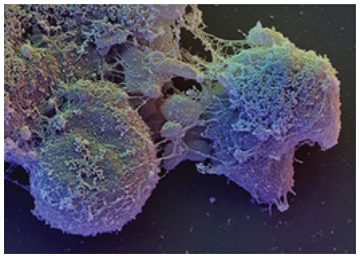


Figure 3.30 Embryonic Stem Cells.
Because they can develop into any type of cell, stem cells offer tremendous therapeutic possibilities.

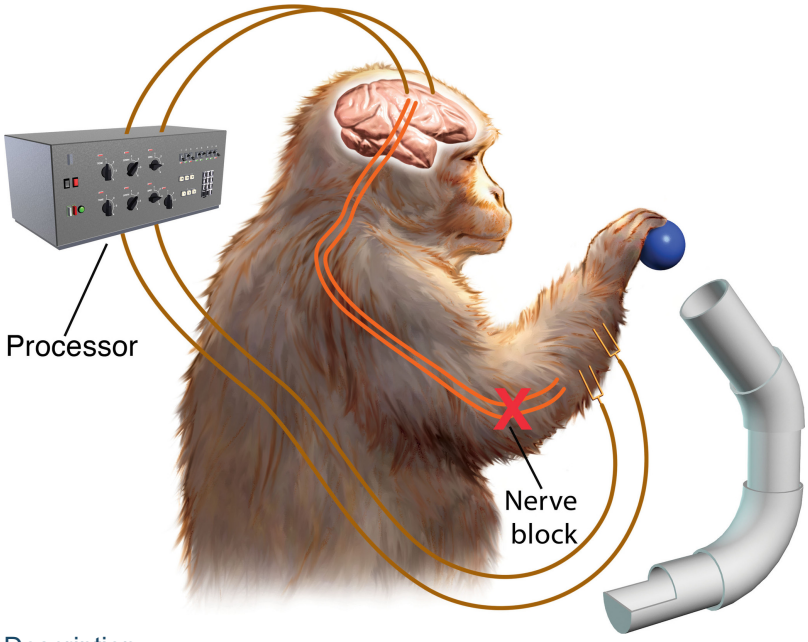
Source: David Scharf/Science Source.

Five years after his injury, Christopher Reeve undertook an intensive rehabilitation program called activity-based recovery (J. W. McDonald et al., 2002). The therapy involved using electrical stimulation to exercise critical muscle groups. For example, electrodes placed over three muscles of each leg were activated sequentially to allow him to pedal a customized exercise bike. This effort appeared futile; no spinal cord patient classified as Grade A (the category of greatest impairment) had ever recovered more than one grade after 2 years. But after 3 years of this therapy, two thirds of Reeve's touch sensation had returned, and he was able to walk in an aquatherapy pool and make swimming movements with his arms; as a result, he was reclassified to Grade C. It even seemed possible that Reeve might achieve his goal of walking again, but he died of heart failure in October 2004. The Christopher Reeve Paralysis Foundation continues his work toward lifting Ramón y Cajal's decree. But because that day appears far off, researchers in the meantime are merging neurons

with electronics to give back to patients control of their bodies (see A Further Look on page 84).

A Further Look:

Mending the Brain With Computer Chips



Description

(a) A Monkey Uses Its Paralyzed Arm to Pick Up and Manipulate a Ball.

Source: Adapted from Figure 1 of "Restoration of Grasp Following Paralysis Through Brain-Controlled Stimulation of Muscles," by C. Ethier, E. R. Oby, M. J. Bauman, and l. E. Miller," *Nature, 485*, pp. 368–371.

(b) A Paralyzed Woman Gives Herself a Drink for the First Time in 15 Years.

Source: Figure 2 of "Reach and Grasp by People With Tetraplegia Using a Neurally Controlled Robotic Arm," by L. R. Hochberg et al., *Nature, 485*, pp. 372–377.

Faced with the daunting challenge of coaxing axons to regrow and stem cells to take over the duties of brain cells, some researchers are turning to computer chips, and their results have been encouraging. For example, neuroscientists at Northwestern University simulated spinal injury in two monkeys by temporarily anesthetizing nerves in their arms at the elbow. Then they used an electrode array to pick up signals from the hand area of the motor cortex, which were then amplified and delivered to muscles in the forearm. With this arrangement, the monkeys were able to grasp and

pick up a ball and drop it into an opening almost as well as they had done before the anesthesia (Figure a; Ethier, Oby, Bauman, & Miller, 2012).

Moving these experimental accomplishments out of the laboratory and into the patient's everyday life will take years, but the potential of brain-computer interfaces (BCIs) is proceeding rapidly. The possibility of using thought to control external devices promises some degree of independence for individuals with limited limb mobility. After implantation of an electrode array in the arm area of his motor cortex, a 25-year-old quadriplegic (both arms and legs paralyzed) was able to move a cursor on a computer screen to read emails and to play a simple computer game (Hochberg et al., 2006). Later refinements have allowed two patients to control a robotic arm to pick up and manipulate objects, including drinking from a water bottle (see Figure b; Hochberg et al., 2012).

Although the ability to accomplish a task in and of itself may seem like an adequate goal, the reality is that being able to accomplish tasks with speed comparable to unimpaired individuals is often a practical limitation for technological advances to be adopted and implemented on a wider scale. A team led by neurosurgeon Jaimie Henderson, working at Stanford as part of the Brain Gate consortium, implanted tiny electrode arrays onto the surface of the motor cortex of individuals who were paralyzed. The volunteers were able to use their brain's motor signals to communicate electronically, typing messages at up to eight words per minute, or about half the speed individuals can type on their cell phones (Pandarinath et al., 2017).

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- Describe the four steps of nervous system development and the fifth step of maturation.
- Give three examples of changes in the brain resulting from experience.
- What are the obstacles to recovery from injury in the CNS and the strategies for overcoming them?

IN PERSPECTIVE

We could end this chapter by talking about how much is known about the brain and its functions. Or we could tell you about how little is known. Either point of view would be correct; it is the classic case of whether the glass is half full or half empty. As we said in Chapter 1, remarkable progress has been made during the past few years. The functions of most areas of the brain are known. We have a good idea of how the brain develops and how neurons find their way to their destinations and make functional connections. And we're getting closer to understanding how the neurons form complex networks that carry out the brain's work.

But questions remain: How does the brain combine activity from widespread areas to bring about an action or a decision or a conscious experience? What is a thought? How do we fix a broken brain? But, of course, there is hope, and for good reason. You will see in the following chapters that a vast amount of knowledge has already been gathered and that researchers have a solid foundation for making remarkable advances in our lifetime and revolutionary ones in yours.

Chapter Summary

The Central Nervous System

- The CNS consists of the brain and the spinal cord.
- The CNS is arranged in a hierarchy, with physically higher structures carrying out more sophisticated functions.
- The cortex is the location of the most sophisticated functions; the convoluted structure of the cerebral hemispheres provides for the maximum amount of cortex.
- See Table 3.2 for the major structures of the brain and their functions.
- Although localization is an important functional principle in the brain, most functions depend on the interaction of several brain areas.
- The spinal cord contains pathways between the brain and the body below the head and provides for sensory-motor reflexes.
- The meninges and the cerebrospinal fluid protect the brain from trauma; the blood-brain barrier blocks toxins and blood-borne neurotransmitters from entering the brain.

The Peripheral Nervous System

- See Figure 3.20 for a summary of the divisions of the nervous system.
    - The PNS consists of the cranial and spinal nerves or, functionally, the somatic nervous system and the ANS.
    - The somatic nervous system consists of the sensory nerves and the nerves controlling the skeletal muscles.
    - The sympathetic branch of the ANS prepares the body for action; the parasympathetic branch conserves and renews energy.
- Interconnection in the sympathetic ganglion chain means that the sympathetic nervous system tends to function as a whole, unlike the parasympathetic branch.

Development and Change in the Nervous System

- Prenatal development of the nervous system involves
    - *proliferation*, the multiplication of neurons by division;
    - *migration*, in which neurons travel to their destination;

    - *circuit formation*, the growth of axons to, and their connection to, their targets; and
    - *circuit pruning*, the elimination of excess neurons and incorrect synapses.
- Myelination continues through adolescence or later, with higher brain levels myelinating last.
- Experience can produce changes in brain structure and function.
- Although some recovery of function occurs in the mammalian CNS, there is little or no true repair of damage by either neurogenesis or regeneration; enhancing repair is a major research focus.

Study Resources

For Further Thought

- Patients with damage to the right parietal lobe, the temporal lobe, or the prefrontal cortex may have little or no impairment in their intellectual capabilities, yet they show deficits in behavior that seem inconsistent for an otherwise intelligent individual. Does this modify your ideas about how we govern our behavior?
- Like the heroes in the 1966 science fiction movie *Fantastic Voyage*, you and your crew will enter a small submarine to be shrunk to microscopic size and injected into the carotid artery of an eminent scientist who is in a coma. Your mission is to navigate through the bloodstream to deliver a lifesaving drug to a specific area in the scientist's brain. The drug can be designed to your specifications, and you can decide where in the vascular system you will release it. What are some of the strategies you could consider to ensure that the drug will enter the brain and be effective?
- What strategy do you think has the greatest potential for restoring function in brain-damaged patients? Why?

Test Your Understanding

1. Describe the specific behaviors you would expect to see in a person with prefrontal cortex damage.
2. Describe compensation and reorganization in recovery from brain damage, giving examples.
3. In what ways does the brain show plasticity after birth?

Select the best answer:

1. Groups of cell bodies in the CNS are called
    1. tracts.
    2. ganglia.
    3. nerves.
    4. nuclei.
2. The prefrontal cortex is involved in all but which one of the following functions?
    1. Responding to rewards
    2. Orienting the body in space
    3. Making decisions
    4. Behaving in socially appropriate ways
3. Because the speech center is usually located in the left hemisphere of the brain, a person with the corpus callosum severed is unable to describe stimuli that are
    1. seen in the left visual field.

2. seen in the right visual field.
3. presented directly in front of him or her.
4. felt with the right hand.

4. A person with damage to the inferior temporal cortex would most likely be unable to
    1. see.
    2. remember previously seen objects.
    3. recognize familiar objects visually.
    4. solve visual problems, such as mazes.
5. A particular behavior is typically controlled by
    1. a single structure.
    2. one or two structures working together.
    3. a network of structures.
    4. the entire brain.
6. When the police have a drunk-driving suspect walk a straight line and touch his nose with his finger, they are assessing the effect of alcohol on the
    1. motor cortex.
    2. corpus callosum.
    3. cerebellum.
    4. medulla.
7. Cardiovascular activity and respiration are controlled by the
    1. pons.
    2. medulla.
    3. thalamus.
    4. reticular formation.
8. All the following are involved in producing movement, except the
    1. hippocampus.
    2. cerebellum.
    3. frontal lobes.
    4. basal ganglia.
9. Damage would be most devastating to humans if it destroyed the
    1. pineal gland.
    2. inferior colliculi.
    3. corpus callosum.
    4. medulla.
10. If the ventral root of a spinal nerve is severed, the person will experience
    1. loss of sensory input from a part of the body.
    2. loss of motor control of a part of the body.
    3. loss of both sensory input and motor control.
    4. none of the above.
11. During a difficult exam, your heart races, your mouth is dry, and your hands are icy. In your room later, you fall limply into a deep sleep. Activation has shifted from primarily _____ to primarily _____.
    1. somatic, autonomic
    2. autonomic, somatic
    3. parasympathetic, sympathetic
    4. sympathetic, parasympathetic
12. In the circuit formation stage of nervous system development,
    1. correct connection of each neuron is necessary, because barely enough neurons are produced.
    2. axons grow to their targets and form connections.
    3. neurons continue dividing around a central neuron, and those neurons form a circuit.
    4. neurons that fail to make functional connections die.
13. Fetal alcohol syndrome involves
    1. loss of myelin.
    2. overproduction of neurons.
    3. errors in neuron migration.
    4. excessive growth of glial cells.
14. The study in which kittens reared in an environment with only horizontal or vertical lines were later able to respond only to stimuli at the same orientation is an example of
    1. compensation.
    2. reorientation.

3. reorganization.
4. regeneration.

15. If a peripheral nerve were transplanted into a severed spinal cord, it would
    1. fail to grow across the gap.
    2. grow across the gap but fail to make connections.
    3. grow across the gap and make connections but fail to function.
    4. bridge the gap and replace the function of the lost neurons.

Answers:

1. d, 2. b, 3. a, 4. c, 5. c, 6. c, 7. b, 8. a, 9. d, 10. b, 11. d, 12. b, 13. c, 14. c, 15. a.

For Further Reading

1. “Reprogrammed Cells Could Tackle Brain Damage,” by Kelly Servick (*Science, 362*, 736–737), reports on new and controversial work claiming to have created neurons from glial cells to repair brain damage in animals.
2. *The Human Brain Book*, by award-winning science writer Rita Carter (DK Publishing, 2014), ranges from brain anatomy and neural transmission to explorations of sex and love, language, thinking, and consciousness. The book comes with an interactive DVD.
3. *The Brain’s Way of Healing*, by Norman Doidge (Viking, 2015), includes eight chapters of research and cases illustrating the brain’s plasticity and ability to recover from losses such as blindness and loss of motor control.
4. *The Man Who Mistook His Wife for a Hat and Other Clinical Tales*, a collection of case studies by Oliver Sacks (Harper Perennial, 1990), is as entertaining as it is informative, as it treats the human side of brain damage and disorder.
5. *The Brain: The Story of You*, by David Eagleman (Vintage, 2017), demonstrates that brain science has the ability to answer questions such as “Who are ‘you’?” “What is reality?” and “How do you make decisions?”
6. Irwin Feinberg answers the question “Why Is Synaptic Pruning Important for the Developing Brain?” in *Scientific American Mind* (May 2017, p. 75).

Key Terms

anterior 57

association area 59

auditory cortex 61

autonomic nervous system (ANS) 69

blood-brain barrier 68

Broca’s area 56

central nervous system (CNS) 52

central sulcus 56

cerebellum 65

cerebral hemispheres 53

cerebrospinal fluid 63

circuit formation 74

circuit pruning 75

compensation 81

corpus callosum 63

cortex 53

cranial nerves 69

dorsal 57

dorsal root 66

fetal alcohol syndrome 75

fissure 53

frontal lobe 56

ganglion 52

growth cone 74

gyrus 53

hydrocephalus 81

hypothalamus 62

inferior 57

inferior colliculi 64

inferior temporal cortex 61

lateral 57

lateral fissure 56

longitudinal fissure 53

medial 57

medulla 65

meninges 68

midbrain 64

migration 73

motor cortex 56

neglect 61

nerve 52

neurogenesis 80

neurotrophins 75

nucleus 52

occipital lobe 62

parasympathetic nervous system 71

parietal lobe 59

peripheral nervous system (PNS) 69

pineal gland 63

plasticity 75

pons 65

posterior 57

precentral gyrus 56

prefrontal cortex 58

primary somatosensory cortex 59

proliferation 73

psychosurgery 59

radial glial cells 73

reflex 67

regeneration 80

reorganization 76

reticular formation 65

somatic nervous system 69

spinal cord 66

spinal nerves 69

stem cells 83

stroke 77

sulcus 53

superior 57

superior colliculi 64

sympathetic ganglion chain 71

sympathetic nervous system 70

temporal lobe 61

thalamus 62

tract 52

traumatic brain injury (TBI) 79

ventral 57

ventral root 66

ventricles 63

visual cortex 62

Wernicke's area 61

Descriptions of Images and Figures

Back to Figure

At 3 weeks, a tubular structure is labeled from top to bottom as follows: Forebrain, midbrain, hindbrain, and spinal cord.

At 7 weeks, the forebrain develops significantly, while the midbrain and the hindbrain develop less significantly. Cranial nerves are present on the hindbrain.

At 11 weeks, the forebrain and the hindbrain develop significantly.

At birth, the midbrain is hidden inside the forebrain, and the hindbrain develops into cerebellum and medulla.

Back to Figure

The center of the brain consists of corpus callosum and anterior commissure. The longitudinal fissure extends vertically along the center of the brain. The white matter around the corpus callosum is enclosed within the cerebral cortex or gray matter. The surface of the cortex is ridged and wrinkled, labeled gyrus, and the groove between the gyri is labeled sulcus. A deep fissure extending to the center of the brain is labeled, lateral sulcus.

Back to Figure

1. Armadillo brain is small and smooth.
2. Monkey brain is larger and consists of few distinct folds on its surface. A small cerebellum is in the hindbrain.
3. Chimpanzee brain consists of multiple distinct folds on its surface. Its cerebellum is larger than that of the monkey brain.

Back to Figure

The brain consists of four lobes. The frontal lobe is at the anterior side of the brain. The parietal lobe is posterior to the frontal lobe and is separated from it by the central sulcus. The temporal lobe is inferior to the frontal lobe and is separated by the lateral fissure. The occipital lobe is at the posterior side of the brain.

The functional areas are as follows:

- Prefrontal cortex at the anterior side of the frontal lobe.
- Broca's area on the inferior side of the frontal lobe.
- Precentral gyrus or motor cortex on the posterior end of the frontal lobe.
- Postcentral gyrus or somatosensory cortex on the anterior end of the parietal lobe.
- Auditory cortex on the superior side of the temporal lobe.
- Wernicke's area on the superior side of the temporal lobe, posterior to the auditory cortex.

- Visual cortex at occipital cortex.

Back to Figure

1. There are two illustrations. The first illustration shows the lateral view of the brain. The orientations are as follows:

    - Anterior: Toward the front.
    - Posterior: Toward the rear.
    - Superior: Toward the top.
    - Inferior: Toward the bottom.
    - Dorsal: Toward the back.
    - Ventral: Toward the stomach.

      The second illustration shows the cross section of the brain. The orientations are as follows:

    - Lateral: Toward the side.
    - Medial: Toward the middle.

2. The illustration shows three planes of cross sections of the brain.

    - Coronal: The plane divides it between front and back.
    - Sagittal: The plane divides it between the sides.
    - Horizontal: The plane divides it between top and bottom.

Back to Figure

The parts are labeled along the cortex and illustrated using parts of a homunculus. The parts from top to bottom are as follows:

- Toes
- Ankle
- Knee
- Hip
- Trunk
- Shoulder
- Elbow
- Wrist
- Hand
- Little finger
- Ring finger

- Middle finger
- Index finger
- Thumb
- Neck
- Brow
- Eyelid and eyeball
- Face
- Lips
- Jaw
- Tongue
- Swallowing

Lips, jaw, and tongue are used for vocalization, jaw and tongue are used for salivation, and tongue is used for mastication.

The hand and face of the homunculus are represented as large structures, and the body, leg, and vocalization organs are represented as smaller structures.
Back to Figure

a. A black-and-white photo shows Walter Freeman surrounded by nurses and men in suits, who observe him driving an instrument between the eyelid and eyeball using a mallet. b. A scan of the brain shows its horizontal view with arrows pointing toward a dark region in the frontal lobe.

Back to image

1. A 3-D image shows the rendering of Gage's skull and his brain. A rod passes up the left cheekbone, through the left eye socket, and through the frontal lobe of the brain.
2. A brain scan shows a white spot in the center of the brain, and multicolored patches along the lateral sides of the brain.
3. A sepia photo of Phineas Gage holding the tamping iron. His left eye is closed.

Back to Figure

The thalamus is at the center of the brain, and is surrounded by the lateral ventricle, which in turn is surrounded by corpus callosum, located inferior to cingulate gyrus. The hypothalamus, located anteroinferior to the thalamus, leads to the pituitary gland. The pineal gland, located posteroinferior to the thalamus, leads to superior and inferior calculi. The midbrain is located inferior to the thalamus, and it leads to pons, medulla, and spinal cord. The cerebellum is located posterior to pons. The frontal lobe, parietal lobe, cerebral cortex, and occipital lobe are labeled.

Back to Figure

1. A patient sits at a table behind a barrier and touches a pair of glasses located on the other side of the barrier.
2. The stimulus from the glasses reaches the visual cortex at the back of the brain in the right hemisphere. The signal from the visual cortex does not reach the language center in the left hemisphere. The patient says, "Pencil?"

Back to Figure

The posterior view and superior cross-section view show the disc anterior to the spinal cord located inside the vertebrae. A nerve root extends from the spinal cord.

The lateral view of the vertebral column shows the classification of nerves as follows:

- Cervical nerves: C 1 to C 8
- Thoracic nerves: T 1 to T 12
- Lumbar nerves: L 1 to L 5
- Sacral nerves: S 1 to S 5
- Coccygeal nerve

Back to Figure

A signal passes through the sensory neuron from hand, spinal nerve, dorsal root ganglion, and reaches the ventral horn through the dorsal root (1). A reflex arc is formed (2), the signal passes through the ventral root of the spinal cord (3), and along the motor neuron of the biceps muscle (4). The signal reaching the ventral horn also travels through the sensory neuron to the brain (5). Signals from motor neuron in the brain reach the ventral horn (6).

Back to Figure

The blood vessel is surrounded by cerebrospinal fluid. The inner wall of the vessel is lined by a layer of endothelial cell with tight junction between the cells that prevent large molecules from passing into the cerebrospinal fluid. Passive diffusion of oxygen (O 2), carbon dioxide (C O 2), fat-soluble substances, and water, and active transport of amino acids and glucose take place between the blood vessel and the fluid.

Back to Figure

The organization chart shows that the nervous system is classified into central and peripheral nervous system. The central nervous system includes brain and spinal cord. The peripheral nervous system is classified into two: somatic and autonomic. Autonomic is further divided into two: Sympathetic and parasympathetic nervous system.

The illustration shows the spinal cord extending from the brain. These form the central nervous system. Branching nerves from the cord, labeled Nerves of peripheral nervous system, extend to all parts of the bodies.

Back to Figure

The cranial nerves are numbered and are accompanied by their name, function, and a corresponding illustration. The nerves are as follows.

1. Olfactory. Sensory: Nose. An illustration of the sagittal view of nose.
2. Optic. Sensory: Eye. An illustration of the eye.
3. Oculomotor. Motor: All eye muscles except those supplied by 4 and 6.
4. Trochlear. Motor: Superior oblique muscles.
5. Trigeminal. Motor: Chewing muscles. Sensory: Face, sinuses, teeth, etcetera. An illustration of the lateral view of the head showing nerves and skull.
6. Abducens. Motor: External rectus muscle. An illustration of the eye and its muscles.
7. Facial. Motor: Muscles of face. An illustration of muscles in the face.
8. Vestibulocochlear. Sensory: Inner ear. An illustration of the inner ear.
9. Glossopharyngeal. Motor: Pharyngeal musculature. Sensory: Posterior part of the tongue, tonsil, and pharynx. An illustration of the sagittal view of nose, mouth, and respiratory tract.
10. Vagus. Motor: Heart, lungs, bronchi, gastrointestinal tract. Sensory: Heart, lungs, bronchi, trachea, larynx, pharynx, gastrointestinal tract, and external ear. An

illustration of the heart between the lungs, stomach, and bowels.
11. Accessory. Motor: Sternocleidomastoid and trapezius muscles. An illustration of the muscles in the neck.
12. Hypoglossal. Motor: Muscles of the tongue. An illustration of the sagittal view of the mouth.

Intermediate nerve. Motor: Submaxillary and sublingual gland. Sensory: Anterior part of tongue and soft palate. An illustration of the tongue.

Nerves 1 and 2 are at the base of the brain, and the other nerves start from the brain stem.
Back to Figure

The functions of the sympathetic nervous system from the top of the spinal cord to the bottom are as follows:

- Dilates pupils.
- Inhibits salivation in the salivary glands.
- Increases heart rate.
- Dilates airways in the lungs.
- Inhibits the organs of the digestive system such as liver, stomach, pancreas, and intestine.
- Constricts peripheral blood vessels.
- Activates sweat glands.
- Stimulates adrenal glands on the kidneys to secrete epinephrine and norepinephrine.
- Contracts rectum.
- Relaxes bladder.
- Stimulates orgasm.

The functions of the parasympathetic nervous system from the top of the spinal cord to the bottom are as follows:

- Constricts pupils.
- Stimulates salivation of salivary glands.
- Slows heart rate.
- Constricts airways in the lungs.
- Stimulates the organs of the digestive system such as liver, stomach, pancreas, and intestine.
- Relaxes rectum in elimination.
- Contracts bladder.
- Stimulates genital arousal.

Back to Figure

1. An illustration shows the closing of the neural tube. Initially, the tube is short with a groove across its middle. As the tube grows, the groove closes, leaving a narrow groove at the top and at the bottom. A line across the top end of the tube is labeled 1, a line across the middle is labeled 4, and the two lines between them are labeled 2 and 3.
2. An illustration shows four numbered cross-sections of the tube cut across the lines from illustration a. 1. A neural plate consists of a neural groove on its surface in the middle and neural fold on either side of the groove. A notochord is inferior to the plate. 2. The neural groove deepens as the angle of the neural fold increases forming neural crest. 3. The neural crest on either side of the groove approach each other to close the tube. Neural crest cells are inferior to the neural crest. 4. The parts from bottom to top are as follows: Notochord, neural tube, neural crest cells, and skin.
3. Three micrographs show a groove in the neural tube, the formation of the neural crest, and the closure of the tube.

Back to Figure

The illustration shows neurons traveling from the inner layer of the brain, through the migration zone, toward the outer layer of the brain. A magnified view of a neuron in the migration zone shows that the leading process and trailing process, extending from the opposite sides of a migrating neuron, are wound around a glial fiber.

Back to Figure

1. Two photos. The first photo shows the hand before surgery. All fingers except the thumb are fused. The second photo shows the hand after surgery. The little finger and the thumb are separated from the other fused fingers. Both photos show a triangle on the thumb, a square on the little finger, and a circle on the fused fingers.
2. Two image shows a brain area. Before surgery, a square, a triangle, and a circle are clustered in a location. After surgery, the triangle is above the square and the circle is to the left of the square.
3. Two graphs show y in centimeters along the horizontal axis, ranging from 3.3 to 4.3 in increments of 0.5, and z in centimeters along the vertical axis, ranging from 9.5 to 10.5 in increments of 0.5. All data are approximate. In the first graph, a square is at (3.6, 10.2), a triangle is at (3.65, 10.2), and a square is at (3.75, 10.23). Each shape is centered at an upright ellipse of similar size. In the second graph, a square is at (3.85, 9.95), a triangle is at (3.8, 10.25), and a square is at (3.55, 10.05). Each shape is centered at an upright ellipse of different sizes. The ellipse around the square is the largest, and the ellipse around the circle is the smallest.

Back to image

1. The illustration shows that wires from a processor are connected from the brain to the arm of a monkey. Signals to the brain pass through the nerve block in the arm, making the monkey to lift a ball and put it in a tube.
2. The photo shows a robotic arm holding a bottle of juice with straw for a paralyzed person to drink. The person is on wheelchair, and a device is positioned on their head.

4 THE METHODS AND ETHICS OF RESEARCH

Oli Scarff/Getty Images News/Getty Images

Science, Research, and Theory

- Theory and Tentativeness in Science
- Experimental Versus Correlational Studies

Concept Check

Research Techniques

- Staining and Imaging Neurons
- Light and Electron Microscopy

A Further Look | Looking Into the Brain

- Measuring and Manipulating Brain Activity
- Brain Imaging Techniques

A Further Look | Scanning King Tut

A Further Look | Growing a Model Brain From Stem Cells

- Investigating Heredity

A Further Look | The Brainbow Connection

Concept Check

Research Ethics

Plagiarism and Fabrication

Protecting the Welfare of Research Participants

Gene Therapy

A Further Look | Can Gene Editing Be Regulated?

Stem Cell Therapy

Concept Check

In Perspective

Chapter Summary

Study Resources

After reading this chapter, you will be able to

4.1 Explain how scientific theories are generated.

4.2 Explain how scientists test hypotheses.

4.3 Describe the differences between correlational and experimental studies.

4.4 Describe the methods that scientists have for studying the role of brain structures in behavior.

4.5 Compare the methods that scientists use to investigate the structure and function of the brain.

4.6 Summarize the ethical protections that are in place for human participants and research animals.

4.7 Examine the ethical concerns that have been raised about stem cell and gene therapy research.

David Vetter, the famous “bubble boy” of the 1970s, was born with *severe combined immunodeficiency (SCID)*, which left him without an immune system and fatally vulnerable to infections. In spite of being reared in the sterile environment of a plastic tent, he grew up as normally as possible. He attended school via telephone, watched football games on TV with his dad, attended a special showing of *Return of the Jedi* in his “bubble,” and played outside briefly in a “space suit” provided by NASA (Figure 4.1). When David was 12, doctors attempted a new procedure for bone marrow transplant from an incompatible donor. His body accepted the transplant, but a virus lurking in the marrow led to lymphoma. He spent his last days in a hospital room, where he was touched and kissed by his mother for the first and last time. A center in

the Texas Children's Hospital now bears his name, where he is remembered for his contributions to immunology and the discovery that cancer can be caused by viruses.

Figure 4.1 David Vetter, the "Bubble Boy."
David doing schoolwork inside his isolation tent during a visit from one of his teachers (outside the bubble).

Courtesy of the Baylor College of Medicines Archives.

Two years later, Ashanti DeSilva was born with SCID. By the time she was 4, her doctors realized that enzyme replacement treatment was no longer working, and she became the first person to receive gene therapy for the disease. The treatment was only partially successful, but she is now living a normal life on a lower enzyme dose. Almost a half century after David was born, eight babies with SCID were treated by removing stem cells from their bone marrow and using deactivated HIV virus to carry healthy genes into the stem cells before returning them to the bone marrow (Mamcarz et al., 2019). Sixteen months later, they had normally functioning immune systems and were gaining weight, promising a safer and more effective cure for SCID.

This is the way science progresses. The evolution of neuroscience is a very human story of failures and triumphs as today's researchers combine their ingenuity with the accumulated knowledge of their predecessors to solve the problems that beset us all. Their accomplishments are also the result of increasingly powerful research methods, including research design as well as technology. This is the story of the role that research methodology plays in the field of neuroscience and of the increasing ethical implications of our advancing knowledge. But first, we need to take a few minutes to review some important points about research in the context of behavioral neuroscience.

SCIENCE, RESEARCH, AND THEORY

Science is distinguished not by the knowledge it produces but *by its method of acquiring knowledge*. We learned in Chapter 1 that scientists' primary method is empiricism; this means that they rely on observation for their information rather than on intuition, tradition, or logic (alone). Descartes started out with the traditional assumption that there was a soul, and then he located the soul in the pineal gland because it seemed the logical place for the soul to control the brain. Aristotle, using equally good logic, had located the soul in the heart because the heart is so vital to

life. (He thought that the brain's function was to cool the blood!) Observation—which is a much more formal activity in science than the term suggests—is more objective than alternative ways of acquiring knowledge; this means that two observers are more likely to reach the same conclusion about what is being observed (though not necessarily about its interpretation) than if they were using intuition, introspection, or logic.

Behavioral neuroscientists, and scientists in general, have great confidence in observation and all the methods in their arsenal. But in scientific writings, you will often see statements beginning with "It appears that…," "Perhaps…," or "The results suggest…." So you might well wonder: *Why do scientists always sound so tentative?*

Theory and Tentativeness in Science

One reason for the tentativeness is that the field is very complex, so it is always possible that a study is flawed or that new data will change how previous studies are interpreted. A second reason is that scientists base their conclusions on samples of participants or research animals and samples of data from those individuals; the laws of probability tell us that even well-designed studies will occasionally include a few unusual participants, or a slight but important shift in behavior may occur that has nothing to do with the variables under study.

? Why are scientists so tentative?

Scientists recognize that knowledge is changing rapidly and the cherished ideas of today may be discarded tomorrow. A case in point is that, until recently, no one accepted that there was regrowth of severed axons or any new neurons born in the adult mammalian central nervous system (Rakic, 1985), beliefs that you now know are incorrect. You seldom hear scientists using the words *truth* and *proof*, because these terms suggest final answers. Such uncertainty may feel uncomfortable to you, but centuries of experience have shown that certainty about truth can be just as uncomfortable. "Certainty" has an ugly way of stifling the pursuit of knowledge.

One way the researcher has of making sense out of ambiguity is through theory. A **theory** integrates and interprets diverse observations in an attempt to explain a phenomenon. For example, researchers noticed that people who overdosed on the drug amphetamine were being misdiagnosed as having schizophrenia when they were admitted to emergency rooms reporting symptoms of hallucinations and paranoia. They also knew that amphetamine increases activity in neurons that release dopamine as the neurotransmitter. This led several research teams to propose that schizophrenia is due to excess dopamine activity in the brain, a finding we will explore in more detail in Chapter 14.

A theory explains existing observations, but it also generates hypotheses that guide further research. One hypothesis that came from dopamine theory was that drugs that decrease dopamine activity would improve functioning in schizophrenia. This hypothesis was testable, which is a requirement for a good theory. The hypothesis was supported in many cases of schizophrenia but not in others. We now realize that the dopamine theory is an incomplete explanation for schizophrenia. However, even a flawed theory inspires further research that will yield more knowledge and additional hypotheses. But remember that the best theory is still only a theory; theory and empiricism are the basis of science's ability to self-correct and its openness to change and renewal.

Now we will examine one of the knottiest issues of research, one that you will need to think about often as you evaluate the research evidence discussed throughout this text.

Experimental Versus Correlational Studies

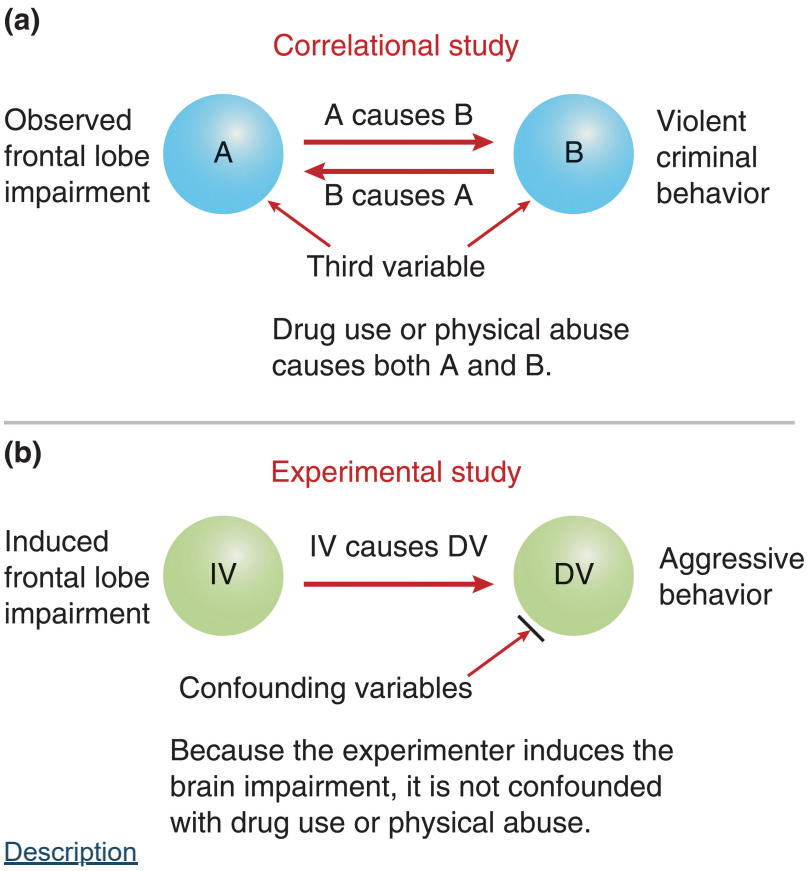
Observation has a broad meaning in science. A behavioral neuroscientist might observe aggressive behavior in children on the playground to see if there are

differences between boys and girls (*naturalistic observation*), report on the brain scan of a patient who had violent outbursts following a car accident that caused brain injury (*case study*), use a questionnaire to find out whether some women are more aggressive during the premenstrual period (*survey*), or stimulate rats' brains with electricity to see which parts control aggressive behavior (*experiment*). All these different research strategies fall into the broad categories of *correlational and experimental studies*.

? What are some advantages of experimental studies over correlational studies?

In an **experimental study**, the researcher manipulates a condition (the independent variable) that is expected to produce a change in the subject's behavior (the dependent variable). The experimenter attempts to eliminate *extraneous variables* that might influence the behavior or equates them across subjects—for example, by removing environmental distractions, instructing participants not to use caffeine or other stimulants beforehand, and "running" subjects at the same time of day. In a **correlational study**, the researcher does not control an independent variable but observes whether two variables are related to each other. When we use brain scans to determine that violent criminals more often have impaired frontal lobe activity, we are conducting a correlational study. If we *induce* the impairment in monkeys (independent variable) and then observe whether this increases aggression (dependent variable), we are performing an experiment.

Figure 4.2 illustrates some of the differences between a correlational and an experimental study of aggressive behavior. Based on observations that violent criminals often have impaired frontal lobe functioning, we might identify a large group of impaired individuals (using brain scans or behavioral and cognitive tests) and see if they have a record of violent crimes. We would very likely find that they do, but Figure 4.2a reveals a problem with interpretation: For all we know, the individuals' brain damage may have been incurred in the process of committing their violent acts, rather than the other way around. Or both frontal lobe damage and violent behavior could stem from any number of third variables, such as physical abuse during childhood, long-term drug use, or a genetic predisposition to engage in risky behaviors. These variables are potentially *confounded* with each other, so we cannot separate their effects. In other words, *we cannot draw conclusions about cause and effect from a correlational study*.



Description

Figure 4.2 Correlational Versus Experimental Studies.
In a correlational study (a), we cannot tell whether *A* influences *B*, *B* influences *A*, or a third variable affects both. In an experimental study (b), the researcher manipulates the independent variable (IV), which increases assurance that it is the cause of the change in the dependent variable (DV). (The red arrows indicate possible interpretations of causation.)

What about doing this research as an experimental study? For ethical reasons, of course, we would not induce brain damage in humans, but remember the study described in Chapter 3 in which researchers used an electromagnetic field to disrupt activity in the visual cortex of blind individuals. Let's use this *transcranial magnetic stimulation* to disrupt temporarily our hypothetical volunteers' frontal lobe functioning. Granted, we won't see them become physically violent in the laboratory, but we can borrow a technique from a similar study we will see later in Chapter 8, on emotion: We will administer several mild shocks to the subject under the pretense that the shocks are being controlled by another (fictitious) player, and we will record the intensity of shocks our participant delivers in retaliation. Because we selected our research participants and induced the brain impairment, we have *controlled* the confounding variables that plagued us in the correlational study. That is, the variables are likely to be similar between the impaired group and an unimpaired control group, especially if we make sure factors such as age and gender are similar between the groups. Now if we see higher levels of shock administered by subjects while their frontal activity is being disrupted, we can be fairly confident that the frontal lobe impairment is *causing* the increase in the aggressive behavior.

Of course, we could quibble about how well this study mirrors real brain damage and violent aggression; the greater control afforded by experimental studies often carries a cost of some artificiality. Experimentation is the most powerful research strategy, but correlational studies also provide unique and valuable information, such as the observation that children of parents who have schizophrenia have a high incidence of the disorder even when they are reared in normal adoptive homes. To advance our

understanding in behavioral neuroscience, we need correlational studies as well as experimental research, but we equally need to be careful about interpreting their results—a point you should keep in mind as we explore various research techniques and as we look at research in later chapters.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

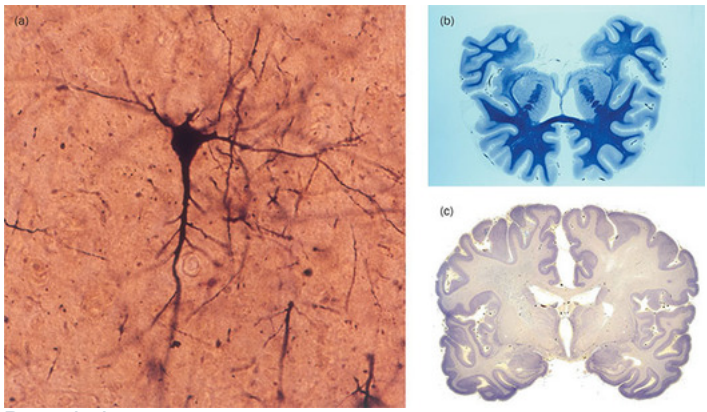
- What is the value of empiricism? What is the value of theory?
- A scientist speaking to a group of students says, “I do not expect my research to find the truth.” Why?
- What advantages do correlational studies have over experiments?
- You hear the newscaster say, “Physicians are urging people to stay active in retirement, because researchers have found that people who are more physically and socially active are less likely to develop Alzheimer’s disease.” What should you be thinking?

RESEARCH TECHNIQUES

The brain does not give up its secrets easily. If we remove a clock from its case and observe the gears turn and the spring expand, we can get a pretty good idea of how a clock measures time. But if we open the skull, how the brain works remains just as much a mystery as before. This is where research technique comes in, extending the scientist’s observation beyond what is readily accessible. Your understanding of the information that fills the rest of this book—and of the limitations of that information—will require some knowledge of how the researchers came to their conclusions. The following review of a few major research methods is abbreviated, but it will help you navigate through the rest of the book, and we will add other methods as we go along.

Staining and Imaging Neurons

It didn’t take long to exhaust the possibilities for viewing the nervous system with the naked eye, but the invention of the microscope took researchers many steps beyond what the pioneers in gross anatomy could do. Unfortunately, neurons are greatly intertwined and are difficult to distinguish from each other, even when magnified. The **Golgi stain** method randomly stains about 5% of neurons, placing them in relief against the background of seeming neural chaos (Figure 4.3a). As we saw in Chapter 2, the Italian anatomist Camillo Golgi developed this technique in 1875, and shortly after, his Spanish contemporary Santiago Ramón y Cajal used it to discover that neurons are separate cells. Golgi and Ramón y Cajal jointly received the 1906 Nobel Prize in physiology and medicine for their contributions.



Description

Figure 4.3 Three Staining Techniques.
(a) Golgi stains highlight individual neurons. (b) Myelin stains emphasize white matter and, therefore, neural pathways (stained blue here). (c) Nissl stains emphasize the cell bodies of neurons (stained dark).

Sources: (a) Walter Dawn / Science Source (b) PROF. J.J. HAUW / Science Source. (c) Reproduced with permission from http://www.brains.rad.msu.edu, and http://brainmuseum.org, supported by the U.S. National Science Foundation.

? What major discovery did Golgi staining enable?

Other staining methods add important dimensions to the researcher's ability to study the nervous system. **Myelin stains** are taken up by the fatty myelin that wraps around axons; the stain thus identifies neural pathways. In Figure 4.3b, the slice of brain tissue is heavily stained in the inner areas where many pathways converge, but it is stained lightly or not at all in the perimeter where mostly cell bodies are located. **Nissl stains** do the opposite; they identify cell bodies of neurons (Figure 4.3c).

Later-generation techniques are used to trace pathways to determine their origin or their destination—that is, which part of the brain is communicating with another. These procedures take advantage of the fact that neurons move materials up and down the axon constantly. For example, if we inject the chemical *fluorogold* into a part of the brain, it will be taken up by the terminals of neurons and transported up the axons to the cell bodies (this is called a retrograde stain). Under light of the appropriate wavelength, fluorogold will fluoresce—radiate light—so it will show up under a microscope and tell us which brain areas receive neural input from the area we injected. For example, fluorogold injected into a rat's superior colliculi will show up a few days later among the light-detecting neurons in the retina.

These staining and tracing procedures reveal fine anatomy, but they do not tell us anything about function. **Autoradiography** makes neurons stand out visibly, just as staining does, but it also reveals which neurons are active, and this information can be correlated with the behavior the animal was engaged in. In this procedure, the animal is injected with a substance that has been made radioactive, such as a type of sugar called 2-deoxyglucose (2-DG). Then the researcher usually stimulates the animal, for instance, by presenting a visual pattern or requiring the subject to learn a task. Active neurons take up more glucose, and because 2-DG is similar to glucose, the neurons involved in the activity become radioactively "labeled." In Chapter 10, you will see an example of this technique, in which vision researchers mapped the projections to the visual cortex from light-receptive cells in the eye (Tootell, Silverman, Switkes, & De Valois, 1982). After injecting monkeys with radioactive 2-DG, they presented the subjects with a geometric visual stimulus. The animals were euthanized (killed painlessly), and a section of their visual cortical tissue was placed on photographic film. The radioactive areas exposed the film and produced an image of the original stimulus. This confirmed that just as the somatosensory projection area contains a map of the body, the visual cortex maps the visual-sensitive retina and, thus, the visual world (Figure 4.4a).

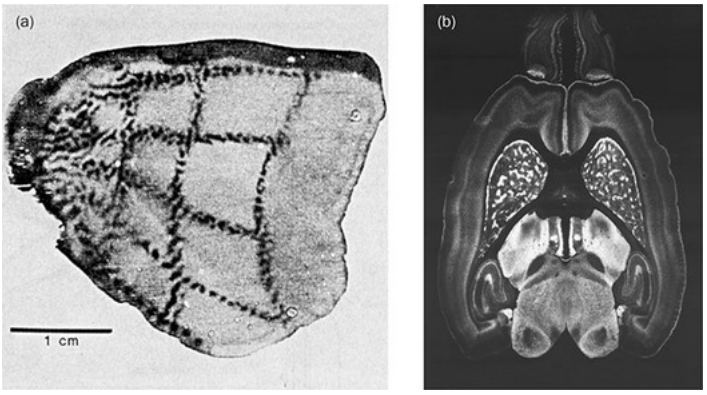


Figure 4.4 Autoradiographs.
(a) Monkeys were injected with radioactive 2-DG before they were presented with a geometric visual stimulus. The monkeys were euthanized, and slices of their brains were placed on photographic film; the pattern of radioactivity produced the image you see here. (b) An autoradiograph of a horizontal slice from a rat's brain that was soaked in a radioactive opiate antagonist, naloxone. White areas indicated opiate receptors. The slice is at the level of the thalamus; the front of the brain is at the top of the picture.

Sources: (a) From "Deoxyglucose Analysis of Retinotopic Organization in Primate Striate Cortex," by R. B. H. Tootell et al., *Science*, 218, pp. 902–904. Reprinted with permission from AAAS. (b) From Herkenham, M. A., & Pert, C. B. (1982). Light microscopic localization of brain opiate receptors: A general autoradiographic method which preserves tissue quality. *Journal of Neuroscience*,2, 1129–1149. Copyright [1982] Society for Neuroscience.

? What advantage does autoradiography have?

A variation of this method is used to determine the location and quantity of receptors for a particular drug or neurotransmitter. Candace Pert used this procedure to find out whether there are receptors in the brain for opiate drugs (a class containing opium, morphine, and heroin), which seemed like the best explanation for the drugs' potency in relieving pain (Herkenham & Pert, 1982; Pert & Snyder, 1973). First, she soaked rat brains in radioactive *naloxone*, a drug that she knew counteracts the effects of opiates, on the assumption that it does so by blocking the hypothesized receptors. She then placed thinly sliced sections of the brains on photographic film. Sure enough, an image of the brain formed, highlighting the locations of opiate receptors (Figure 4.4b). This procedure not only established that the receptors exist but also suggested that the brain makes its own opiates!

Instead of using radioactivity, **immunocytochemistry** uses antibodies attached to a dye to identify cellular components such as receptors, neurotransmitters, or enzymes. The technique takes advantage of the fact that antibodies, which attack foreign intruders in the body, can be custom designed to be specific to any cellular component. The dye, which is usually fluorescent, makes the antibodies' targets visible when the tissue is removed and examined under a microscope. Night-migrating birds use the earth's magnetic field to navigate, and earlier evidence suggested that the magnetic detectors might be *cryptochromes*, which are molecules found in some neurons in the birds' retinas. Henrik Mouritsen and his colleagues (2004) in Germany have provided strong supporting evidence. Using immunocytochemistry, they found that during the day, cryptochromes were plentiful in the retinas of both garden warblers and zebra finches; at night, however, cryptochromes diminished virtually to zero in the nonmigratory finches but *increased* in the eyes of the night-migrating warblers (Figure 4.5).

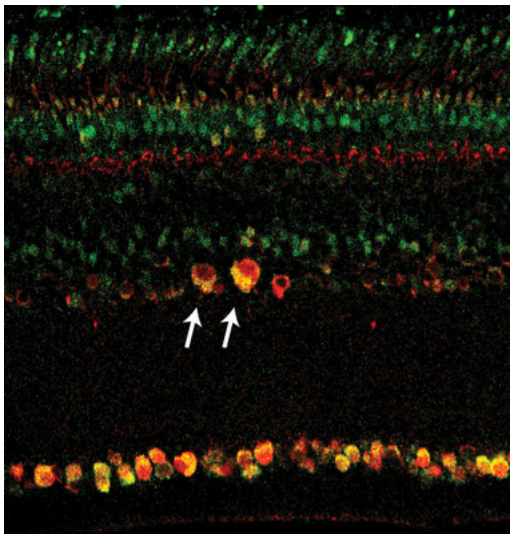


Figure 4.5 Immunocytochemistry Reveals Cryptochromes in the Eyes of Migrating Birds.
Neurons that contain cryptochromes and are currently active are labeled in orange. The larger type of neurons (indicated by arrows) project to a brain area that responds to magnetic field stimulation.

Source: From "Cryptochromes and Neuronal-Activity Markers Colocalize in the Retina of Migratory Birds During Magnetic Orientation," by H. Mouritsen et al., *PNAS, 101*, pp. 14294–14299. © 2004 H. Mouritsen. Used with permission.

But before they could do this study, Mouritsen's team had to decide which of two kinds of cryptochrome to focus their efforts on, CRY1 or CRY2. So they used another powerful research technique that determines where particular genes are active, in this case the *cry1* and *cry2* genes. Remember from Chapter 1 that genes control the production of proteins; the instructions for protein production are carried from the nucleus into the cytoplasm of a cell by **messenger ribonucleic acid (mRNA)**, which is a copy of one strand of the gene's DNA. So when we locate specific mRNA, we know that the gene is active in that place; this is done by in situ hybridization. **In situ hybridization** involves constructing strands of complementary DNA, which will dock with strands of mRNA. Because the complementary DNA is first made radioactive, autoradiography can then be used to determine the location of gene activity (Figure 4.6). The researchers found that the protein product CRY2 was being constructed in cell nuclei, whereas CRY1 was being constructed outside the nucleus. Because a magnetoreceptor was more likely to function outside the nucleus, they limited their study to that cryptochrome.

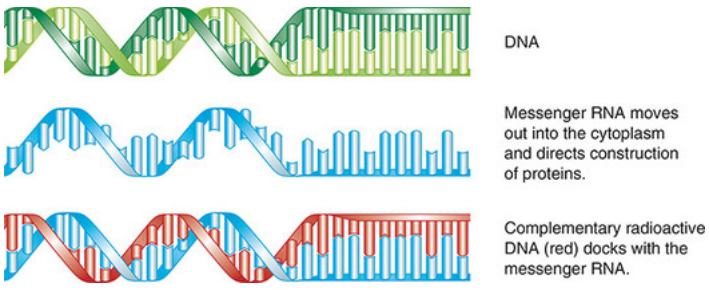


Figure 4.6 DNA, Proteins, and In Situ Hybridization.
Messenger RNA copies a strand of the DNA and then moves out into the cytoplasm, where it controls the development of proteins. Complementary DNA that is radioactive helps researchers locate gene activity.

Light and Electron Microscopy

For more than three centuries, the progress of biological research closely paralleled the development of the light microscope. The microscope evolved from a device that used a drop of water as the magnifier, to the simple microscope with a single lens, to the compound microscope with multiple lenses. At that point, investigators were able to see the gross details of neurons: cell bodies, dendrites, axons, and the largest organelles. But the capability of the light microscope is limited, not due to the skills of the lens maker but due to the nature of light. Increases in magnification beyond about 1,500 times yield little additional information.

The electron microscope, by contrast, magnifies up to about 250,000 times and can distinguish features as small as a few hundred millionths of a centimeter. The **transmission electron microscope** works by passing a beam of electrons through a thin slice of tissue; different parts of the tissue block or pass electrons to different degrees, so the electrons produce an image of the object on a computer screen. It uses magnets to bend the electron beams to magnify the image up to 50 million times; this allows us to see details such as the synaptic vesicles in an axon terminal. Engineers have enhanced the technique in the **scanning electron microscope**. The beam of electrons induces the specimen to emit electrons itself, and these are captured, just as the conventional microscope collects reflected light. Magnification is limited to 2 to 3 million times, but the images have a three-dimensional (3-D) appearance that is helpful in visualizing details. You can see this feature in Figure 4.7, as well as in Figure 2.16.

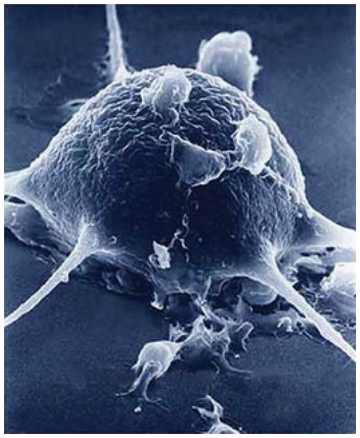


Figure 4.7 Scanning Electron Micrograph of a Neuron.
Notice the depth and detail this kind of imaging provides. (The white structures on and around the cell body are glial cells.)

© Dr. Robert Berdan, 2007.

Microscopic technology continues to evolve, for example, in the *confocal laser scanning microscope* and the *two-photon microscope*. These microscopes image specific kinds of tissue, depending on the fluorescent dye staining the tissue (a fluorescent dye emits light when radiated with light within a specific range of wavelengths). These microscopes have the advantage that they are not limited to very thin slices of tissue. They can be used with thicker tissue samples and can even image details in the upper layers of the exposed living brain; with optical probes, they can image neurons as deep as 1 centimeter below the surface. As an example, researchers using a dye specific for calcium were able to measure movement-related neural activity in the brains of mice running on a treadmill (Dombeck, Khabbaz, Collman, Adelman, & Tank, 2007). As revealed in A Further Look, techniques for viewing the brain are getting a significant boost.

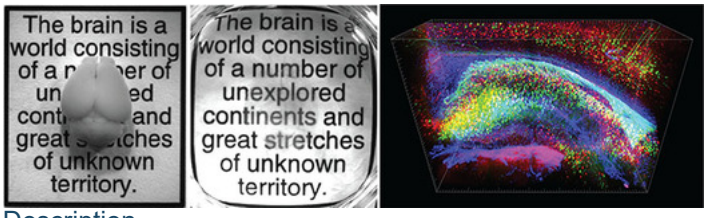
A Further Look:

Looking Into the Brain

Neuroscientists have many holy grails, and one of them is the ability to peer into the brain, to visualize the neurons and their all-important connections. Chapter 2 described methods for imaging white-matter pathways, but the resolution is poorer than researchers would like. Light microscopy provides more detail, but brain tissue is mostly opaque, so it must be sliced into very thin sections that limit the ability to trace pathways. There have been attempts to make brain tissue transparent by extracting the lipids that make up the cell membranes, but the process also removes proteins, and the cells fall apart.

Now a team at Stanford University led by psychiatrist and bioengineer Karl Deisseroth has come up with a solution in the form of a process they call, appropriately, CLARITY (Chung et al., 2013; Tomer, Ye, Hsueh, & Deisseroth, 2014). The brain is placed in a solution of acrylamide, which binds to the brain's proteins and holds them together while the lipids are removed. By then, the tissue is totally transparent, as you can see in the figure. In the next step, the neurons are "labeled" with fluorescent antibodies, which attach to specific proteins and make particular structures visible; the third panel of the figure shows the neurons in an intact mouse hippocampus (the curved structure in the image). The procedure has allowed the team to visualize lesions in the brain of a deceased Alzheimer's patient (K. Ando et al., 2014). The acrylamide increases the tissue's resilience, so that the labels can be removed and replaced with others to highlight different types of neurons. This means that the precious few brains available from people with particular disorders can be used over and over again.

The journal *Science* named CLARITY one of the top 10 breakthroughs of 2013; its potential is being realized in a variety of ways, including visualizing the brains of deceased patients with Alzheimer's disease, Parkinson's disease, autism, and epilepsy (Surat, n.d.). For example, a Caltech research team headed by Viviana Gradinaru (C. Xiao et al., 2016) used the technique to identify circuits of neurons involved in controlling motor activity that is commonly dysfunctional in people with Parkinson's disease. Then, using optogenetic techniques (see pp. 104–105), they were able to show that activation of these circuits could regulate the impaired motor function, paving the way for implanting stimulators into the brains of patients so that they can lead more productive lives with fewer motor impairments.



Description

The first two images compare a mouse brain before and after clarification. The third image is a three-dimensional view of a hippocampus (the curved structure) stained to reveal neurons (green), connecting interneurons (red), and glia (blue).

Source: Reprinted by permission from Macmillan Publishers Ltd. From "Structural and Molecular Interrogation of Intact Biological Systems," by Kwanghun Chung et al., *Nature*, 497, pp. 332–337, doi:10.1038/nature1210. Copyright 2013.

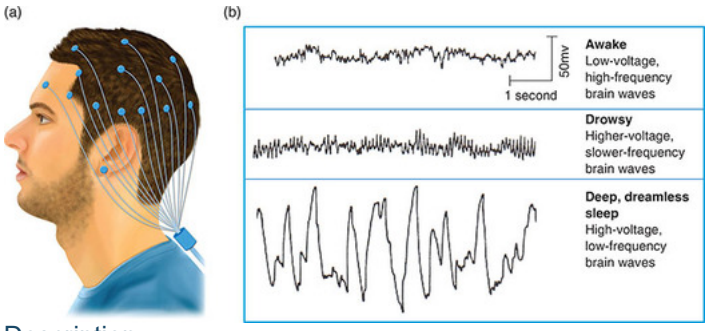
Measuring and Manipulating Brain Activity

You learned in previous chapters that it is easy to stimulate the surface of the brain with electricity to produce movement, sensations, and even apparent memories. We

can also record electrical activity from the surface of the brain or even from the scalp. Studying deeper structures will require more inventive techniques, which we will look at after we discuss electroencephalography.

Electroencephalography

In 1929, the German psychiatrist Hans Berger invented the electroencephalograph and used it to record the first electroencephalogram from his young son's brain. Since then, the technique has proved indispensable in diagnosing brain disorders such as epilepsy and brain tumors; it has also been valuable for studying brain activity during various kinds of behavior, from sleep to learning. The **electroencephalogram (EEG)** is recorded from two electrodes on the scalp over the area of interest; an electronic amplifier detects the combined electrical activity of all the neurons between the two electrodes (popularly known as "brain waves"; see Figure 4.8). Usually, the researcher applies a number of scalp-mounted electrodes and monitors activity simultaneously across multiple brain areas.



Description

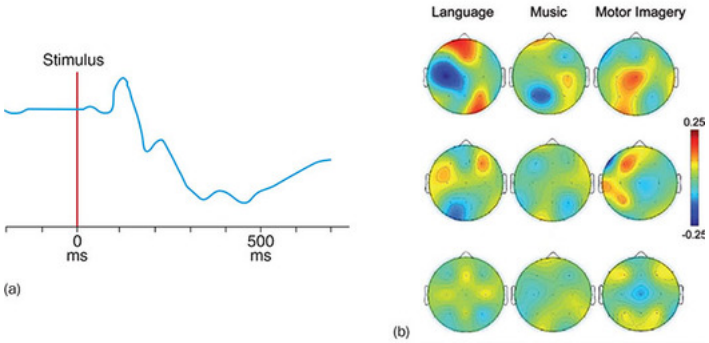
Figure 4.8 An Electroencephalograph and a Sample EEG.
An electroencephalograph records the electrical activity of the brain through electrodes applied to the scalp (a). The up-and-down fluctuations of the tracings on the computer screen (b) indicate the EEG frequency, and the height indicates the voltage. A computer does precise analyses of the signal for research or diagnostic purposes.

Source: (b) From *Current Concepts: The Sleep Disorders*, by P. Hauri, 1982, Kalamazoo, MI: Upjohn.

The *temporal* (time) *resolution* of the EEG is one of its best features; it can distinguish events only 1 millisecond (ms) apart in time, so it can track the brain's responses to rapidly changing events. However, its *spatial resolution*, or ability to detect precisely where in the brain the signal is coming from, is poor. This problem can be alleviated somewhat by applying electrodes directly to the brain, which removes the interference of the skull. Of course, this procedure is used only with animals or with humans undergoing surgery for medical reasons. So although the EEG provides relatively gross measurements, its advantages are good time resolution, ease of use, and lower cost than the imaging techniques we will consider shortly.

EEGs are most useful for detecting changes in arousal, as in the example in Figure 4.8. They are not good at detecting the response to a brief stimulus, such as a spoken word; the time resolution is adequate, but the "noise" of the brain's other ongoing activity drowns out the response, so the tracing looks much like the "awake" recording in the figure. However, by combining electroencephalography with the computer, the researcher can average the EEG over several presentations of the stimulus to produce an **event-related potential**, like the one in Figure 4.9a. Averaging over many trials cancels out the ongoing noise, leaving only the unique response to the stimulus. In this example, Shirley Hill (1995) repeatedly presented a low-pitched tone to her research participants and occasionally interjected a high-pitched tone. Averaging showed a large dip in the electrical potential following the novel (high-pitched) stimulus. In Chapter 5, you will learn that this dip is smaller in

alcoholics than in nonalcoholics, as well as in the young children of alcoholics, which suggests an inherited vulnerability to alcoholism. Another example is that behavioral neuroscientists have used the technique to confirm that spoken words produce a greater response in the left hemisphere, just as you would expect, than in the right hemisphere. Computer processing can also be used to generate images showing the location of activity in the brain and, by adding color coding, the relative intensity of the activity. This enhancement has been invaluable in research, and it has potential uses in medical applications as well. Figure 4.9b is an example from researchers' attempt to develop a means of assessing level of consciousness in patients who had suffered traumatic brain injury.



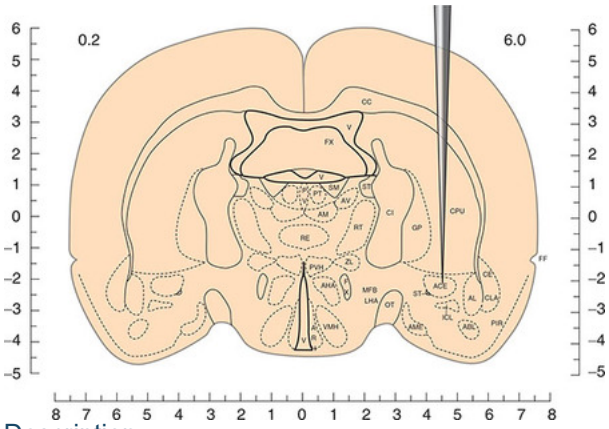
Description

Figure 4.9 Computer Processing of EEG Data.
(a) Averaging EEG over several trials cancels out "noise," leaving an event-related potential, the large dip that occurs when an occasional novel stimulus is inserted among a series of identical stimuli. (b) Computer imaging of EEG activity from numerous electrodes can reveal level of consciousness. These images show the responses to three kinds of stimulation from a normal volunteer (top row), a minimally conscious patient (middle row), and a patient in a coma (bottom row).

Source: (b) From Figure 3 in "Early Detection of Consciousness in Patients With a Severe Traumatic Brain Injury," by Brian L. Edlow et al., *Brain, 140,* pp. 2399–2414. © Oxford Academic, 2017.

Stimulation, Recording, and Stereotaxic Techniques

Most of the structures of interest to brain scientists are well below the surface of the brain; reaching them requires the use of various kinds of electrical, chemical, and light probes. Usually this work is done with animals, and the researcher uses a map of the brain called a *stereotaxic atlas* to determine where to locate the probe. To construct an atlas, first, a large number of brains are sliced into very thin coronal sections; drawings are prepared that show the average location of brain structures on each section (Figure 4.10). The researcher typically uses a **stereotaxic instrument**, a device that allows precise positioning of an electrode or other probe in the brain. Figure 4.11 shows a stereotaxic instrument for rats; the instrument secures the anesthetized rat's head and allows the investigator to insert the probe through a small hole drilled in the skull at the precise location and depth specified by the atlas.



Description

Figure 4.10 A Plate From a Stereotaxic Atlas of the Rat Brain.
Each drawing is numbered to indicate the anterior/posterior location of the slice and the structures shown; the scales on the bottom and the sides of the drawing tell the researcher how far from the midline and how deep to insert the probe. (The electrode from Figure 4.11 is shown superimposed over the drawing, for illustrative purposes.)

Source: L. J. Pellegrino, A. S. Pellegrino, and A. J. Cushman, *A Stereotaxic Atlas of the Rat Brain*, 2nd edition, Kluwer Academic/Plenum Publishers. © 1979; with kind permission from Springer Science+Business Media B.V.

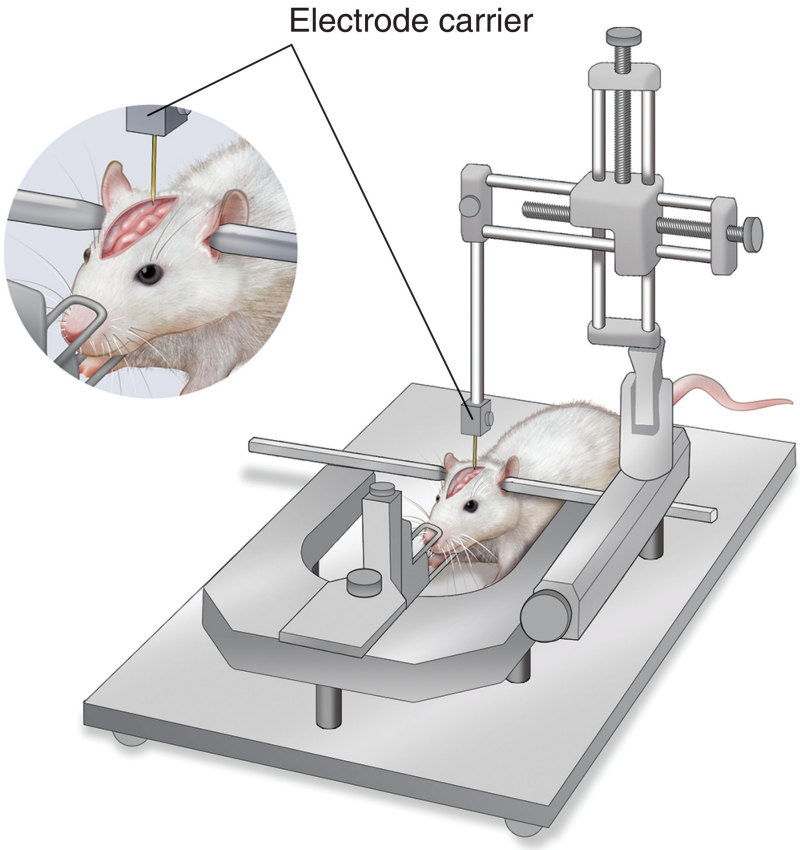


Figure 4.11 A Stereotaxic Instrument.
This device allows the researcher to locate an electrode precisely at the right horizontal position and depth in the animal's brain. (Although its eyes are open, the rat is deeply anesthetized.)

? What are the different ways a stereotaxic instrument is used?

Often the probe is a fine-wire electrode, electrically insulated except at its tip, that is used to activate the structure with very low-voltage electricity. While the still-anesthetized animal's brain is being stimulated, the researcher can monitor responses in other parts of the brain or in the body. If the animal must be awake to test the effect, the electrode can be anchored to the skull; the wound is closed, and after a couple of days of recovery, the rat's behavior can be observed during stimulation. In Chapter 5, you will learn about research in which animals were willing to press a lever to deliver electrical stimulation to certain parts of their own brains. (The stimulation isn't painful, because the brain lacks pain receptors.)

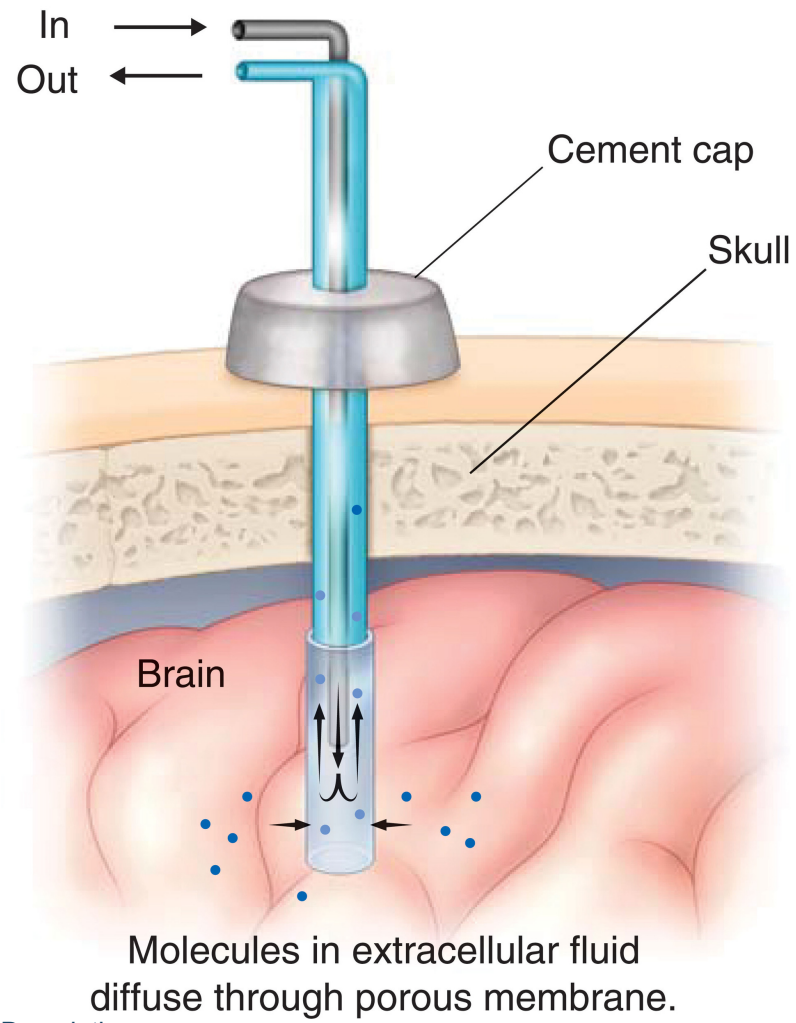
A similar electrode arrangement is used to record neural activity; the researcher might subject the animal to a learning task, present visual or auditory stimuli, or introduce a member of the other sex while monitoring activity in an appropriate brain location. Electrodes ordinarily will record from all the surrounding neurons, but *microelectrodes* have tips so fine that they can be inserted into an individual neuron. Most microelectrodes are glass micropipettes filled with a solution that is similar to the intracellular fluid of the cell and electrically conducting. The tip can be as small as 1 micron (millionth of a meter). Stimulating and recording electrodes may be placed in the brain temporarily in an anesthetized animal, or they may be mounted in a socket cemented to the animal's skull to permit recording in the unanesthetized, behaving subject.

Optogenetic techniques (see Chapter 2) have significant advantages over electrical stimulation. The light-sensitive channels can be inserted in specific types of neurons, so the procedure offers more precise control than electrical stimulation, which activates all neurons in the area. And unlike electrical stimulation, light activation doesn't interfere with simultaneous recording of the resulting neural activity. Neurons near the brain's surface can be stimulated through an opening in the skull, or the light can be directed to deeper structures via optical fibers. Both techniques allow the study of awake, freely moving subjects. The channels are usually introduced by inserting genes from algae or bacteria. Channels derived from these sources are activated by opsins, the same light-sensitive proteins that enable our eyes to detect light; in the original hosts, their roles include orientation to light and control of day-night rhythms, as well as vision (F. Zhang et al., 2011). Optogenetics is not limited to stimulation; by genetically introducing the appropriate sensors, researchers can detect and measure several aspects of neural activity, including membrane voltage, neurotransmitters, and release of transmitters from vesicles (Mancuso et al., 2010; Treger, 2015).

Optogenetics has turned out to be a very powerful technique. It has been used to study the neural bases of brain activities ranging from movement regulation to memory, the role of rhythmic neural activity in behavior and information processing, and the contribution of neural activity to myelination and adult neurogenesis (Deisseroth, 2015). It is also helping us understand the recovery processes following stroke, as well as a wide range of disorders, including Parkinson's disease, Alzheimer's disease, anxiety, depression, and addiction (Deisseroth, 2015; Steinberg, Christoffel, Deisseroth, & Malenka, 2015). Therapeutic applications are on the horizon as well. In 2016, RetroSense Therapeutics completed the first clinical trial establishing the safety of injecting light-sensitive algae into patients' eyes in hopes of restoring some vision to blind individuals ("RetroSense Therapeutics Completes Low Dose Cohort…," 2016).

Chemical stimulation of the brain can be carried out by inserting a small-diameter tube called a cannula. Chemical stimulation has a special advantage over electrical stimulation in that it acts only on neurons with receptors for the chemical. This means that the researcher can simulate the effects of a particular neurotransmitter or block a transmitter's effects at the synapses. Often the tube is not used to deliver the drug but is cemented in place and used later as a guide for inserting a smaller drug-delivery cannula; this arrangement can be used for multiple applications of the chemical over an extended period of time. The same technique is used for microdialysis, in which brain fluids are extracted for analysis, but a more elaborate dual cannula is required. As Figure 4.12 shows, the brain fluids seep through a

porous membrane into the lower chamber of the cannula; an isotonic saline fluid pumped in through the inner tube flows out through the outer tube, taking substances such as neurotransmitters with it for analysis. In Chapter 5, you will see results from both techniques, when researchers deliver drugs of abuse to rats' brains or monitor the release of brain neurotransmitters after an animal is injected with a drug.



Description

Figure 4.12 A Cannula for Microdialysis.
Neurochemicals in the surrounding fluid diffuse into the cannula through the porous membrane. Fluid is pumped in through the inside tube and flows out through the outer tube, carrying the neurochemicals with it.

Carolina Hrejsa/Body Scientific Intl.

Some clinical situations require doctors to insert a probe (an electrode or cannula) into the brain of a human patient—for example, to distinguish between healthy and diseased areas prior to brain surgery, to lesion malfunctioning tissue in patients with epilepsy, or to stimulate the brain in patients with Parkinson's disease (as in Figure 4.13). Stereotaxic atlases of the human brain are published for this purpose, and there are human stereotaxic instruments as well, usually designed to fixate the head, but placement can also be done visually, using one of the brain scanning techniques. Sometimes, a patient undergoing brain surgery will volunteer to have unrelated measurements done at the time for research purposes.

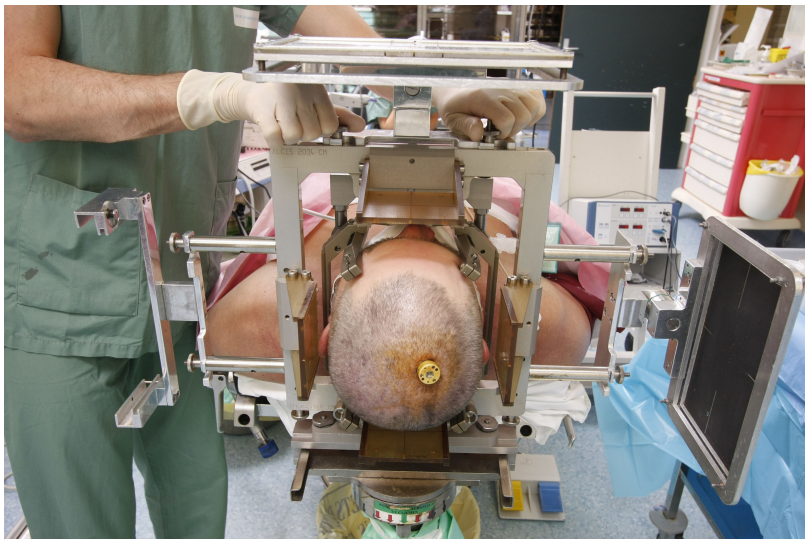


Figure 4.13 A Patient in a Stereotaxic Instrument With an Implanted Stimulator to Treat Parkinson's Disease.

ASTIER - CHRU LILLE / BSIP / Alamy Stock Photo

Ablation and Lesioning

Historically, one of the most profitable avenues of brain research has been the study of patients who have sustained brain damage. Brain damage can occur in a variety of ways: gunshot wounds, blows to the head, tumors, infection, toxins, and strokes. Although these "natural experiments" have been extremely valuable to neuroscientists, they also have major disadvantages. Most important, the damage doesn't coincide neatly with functional areas; it will affect a smaller area or overlap with other functional areas. When neuroscientists study a large number of patients with varying patterns of damage, they are able to identify the location of damage common to people with similar deficits.

Because of these and other difficulties in studying patients with brain damage, researchers have used surgical procedures to produce localized damage in animals. These procedures fall into two categories: ablation and lesioning. **Ablation**, the surgical removal of brain tissue, is usually reserved for large areas of the brain and is typically done using aspiration. In this technique, a vacuum is applied through a micropipette to suck out a targeted area of the brain. **Lesioning**, or surgical damage to neural tissue, is more frequently used due to its precision. Lesions can be produced using electrical current, heat, or a chemical or by using a microscalpel to sever connections. "Reversible lesions," produced by using a chemical that has a temporary effect or by chilling the brain area to suppress neural activity, allow the experimenter to observe behavior before and after the procedure to determine the brain area's function. One problem in interpreting the results of surgical manipulation is that behavior may be controlled by another brain area that relies on the targeted area for inputs or uses the target area as an output area.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technique that uses a magnetic coil to induce a voltage in brain tissue. The device is held close to the scalp over the target area, as in Figure 4.14. TMS is pulsed at varying rates; frequencies of 1/s or lower decrease brain excitability, and frequencies of 5/s or higher increase excitability.

Figure 4.14 A Therapist Uses TMS With a Patient.

Source: "Using Magnets as a Depression Treatment," *Design News*, October 11, 2010. Retrieved August 26, 2012, from http://www.designnews.com/document.asp?doc_id=229440.

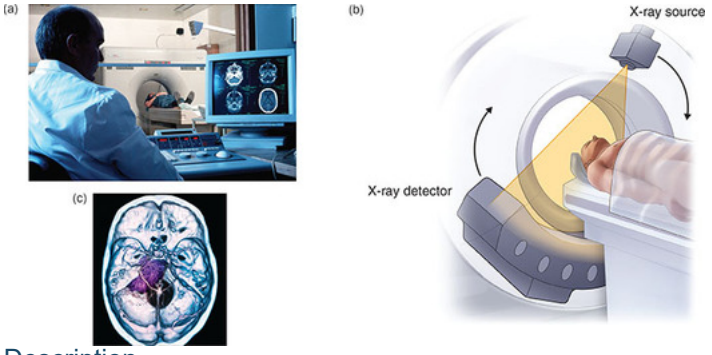
TMS has demonstrated its usefulness mostly as a research instrument. By making clever combination of TMS stimulation and brain imaging techniques (described in the next section), researchers have teased out the neural modifications that account for recovery in stroke patients (Gerloff et al., 2006) and confirmed that making visual-spatial judgments involves not just the parietal area but rather a broader network that includes frontal regions (A. T. Sack et al., 2007). Clinically, TMS has shown effectiveness in treating the symptoms of Parkinson's disease (Chou, Hickey, Sundman, Song, & Chen, 2015), depression and pain (Lefaucheur et al., 2014), and migraine headache (Bhola et al., 2015).

A simpler and less expensive alternative, transcranial direct current stimulation (tDCS), involves application of direct current electrical stimulation through electrodes placed on the scalp (Sparing & Mottaghy, 2008). Unlike TMS, tDCS does not excite neurons to fire. Instead, it activates astrocytes (Monai et al., 2016), increasing neuronal excitability and functional connectivity (Cosmo et al., 2015). Studies indicate that it can improve attention (Coffman, Trumbo, & Clark, 2012) and memory (Prehn-Kristensen et al., 2014). The U.S. military reportedly is experimenting with tDCS for improving training and enhancing performance (E. Young, 2014).

Brain Imaging Techniques

In Broca's day, and, in fact, until fairly recently, a researcher had to wait for a brain-damaged patient to die in order to pinpoint the location of the damage. There was little motivation to do exhaustive observations of the patient's behavior when the patient might outlive the researcher or the body might not be available to the researcher at death. All that changed with the invention of imaging equipment that could produce a picture of the living brain showing the location of damage.

The first modern medical imaging technique came into use in the early 1970s. **Computed tomography (CT)** scanning produces a series of X-rays taken from different angles; a computer combines the series of two-dimensional horizontal cross sections, or "slices," so that the researcher can scan through them as if they are a 3-D image of the entire organ (Figure 4.15). "False colors" are often added to the achromatic image to make features more distinguishable. Imaging soft tissue such as the brain requires injecting a dye that will show up on an X-ray; the dye diffuses throughout the tiny blood vessels of the brain, so it is really the differing density of blood vessels that forms the image. A major drawback of earlier equipment was its extreme slowness, but newer models of CT scanners are fast, and they provide detailed images. CT scans are also popularly known as *CAT scans*.

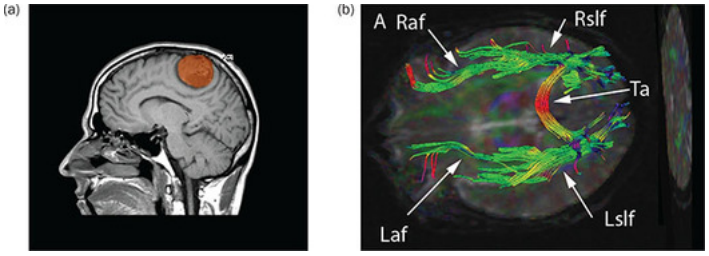


Description

Figure 4.15 Computed Tomography Scanning Procedure.
(a) The patient's head is positioned in a large cylinder, as shown here. (b) An X-ray beam and X-ray detector rotate around the patient's head, taking multiple X-rays of a horizontal slice of the patient's brain. (c) A computer combines X-rays to create an image of a horizontal slice of the brain. The scan reveals a tumor on the right side of the brain.

Sources: (a) Phanie/Science Source. (c) ZEPHYR/SCIENCE PHOTO LIBRARY/Getty Images.

Another imaging technique, **magnetic resonance imaging (MRI)**, works by measuring the radio-frequency waves emitted by the nuclei of hydrogen atoms when they are subjected to a strong magnetic field. Most of that hydrogen is in the water that composes 78% of the brain, but the water content varies in different brain structures, so these emissions from hydrogen nuclei can be used to form a detailed image of the brain (Figure 4.16a). The MRI is reasonably fast, and it can image small areas. Recent increases in power permit more versatile imaging by detecting elements other than hydrogen, including sodium, phosphorus, carbon, nitrogen, and oxygen. MRI scanners can cost up to $3 million and require a suite costing hundreds of thousands more, but more sensitive magnetic field detectors are making low-power, portable scanners available for use in the field. A variant of MRI, **diffusion tensor imaging (DTI)**, measures the movement of water molecules; because water moves easily along the length of axons, this technique is useful for imaging brain pathways and measuring their quality (Figure 4.16b). As you read through the rest of this text, you will learn how the ability to quantify white matter is helping us understand mental and developmental disorders and psychological functions such as intelligence and learning.



Description

Figure 4.16 Magnetic Resonance and Diffusion Tensor Images.
(a) A magnetic resonance image, which has detected a tumor (area highlighted in red). (b) A diffusion tensor image reveals fibers connecting frontal, parietal, temporal, and occipital areas. Colors have been added to provide three-dimensional information; for example, the yellow fibers are ascending or descending vertically.

Sources: (a) © Living Art Enterprises/Photo Researchers/Getty Images. (b) Courtesy of Aaron Filer, MD, PhD.

CT and MRI added tremendous capability for detecting tumors and correlating brain damage with behavioral symptoms. However, CT and MRI lack the ability to detect changing brain activity (as EEG does, for instance). The two remaining techniques add that capability.

Positron emission tomography (PET) involves injecting a radioactive substance into the bloodstream, which is taken up by parts of the brain according to how active they are. The scanner captures the positrons emitted by the radioactive substance to form an image that is color coded to show the relative amounts of activity (Figure 4.17). Radioactive 2-DG is often the substance that is injected because increased uptake of 2-DG by active neurons provides a measure of metabolic activity. Other radioactive substances can be used to monitor blood flow or oxygen uptake, and if a neurotransmitter is made radioactive, it can be used to determine the locations and numbers of receptors for the transmitter. Usually, the researcher produces a "difference scan" by subtracting the activity occurring during a neutral control condition from the activity that occurred during the test condition; this produces an image that uses a color scale to show where activity increased or decreased in the brain.

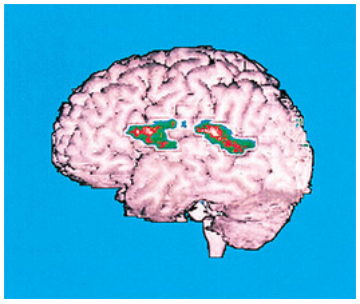


Figure 4.17 Positron Emission Tomography.
A PET scan detects concentrations of radioactivity where neural activity is high; the computer produces a color-coded image, shown here superimposed over a separate scan of a brain. Traditionally, red indicates the greatest amount of activity, followed by yellow, green, and then blue. The individual was working on a verbal task, so areas involved in language processing were activated.

Source: WDCN/Univ. College London / Science Source.

PET equipment is expensive and requires a sophisticated staff to operate it; the facility must also be near a cyclotron, which produces the radioactive substance, and there are few of those around. The advantage that justifies this expense is that PET is able to track changing activity in the brain. However, PET cannot detect changes during behaviors that are briefer than 30 seconds. PET also does not image the brain tissue itself, so the results are often displayed overlaid on a brain image produced by another means, such as MRI.

? What advantage do PET and fMRI have over CT and MRI?

A modification of MRI takes advantage of the fact that blood flow increases in areas of increased neural activity and oxygenated blood has magnetic properties that are different from those of blood that has given up its oxygen to cells. **Functional**

magnetic resonance imaging (fMRI) measures brain activation by detecting increases in blood flow and in oxygen usage in active neural structures (Figure 4.18). MRI and fMRI have the advantage over PET and CT because they involve no radiation, so they are safe to use in studies that require repeated measurements. In addition, fMRI measures activity, like PET, and produces an image of the brain with good spatial resolution, like MRI; researchers can detect activity in cortical areas as small as 1 millimeter (Barinaga, 1997). The fMRI machines are particularly pricey, though, which limits their usefulness for research. The techniques described here are summarized in Table 4.1.

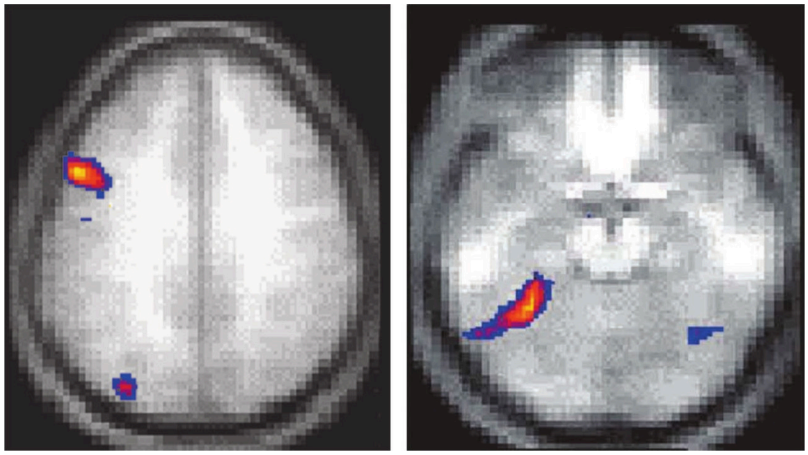


Figure 4.18 An fMRI Scan.
The colored areas were more active when research participants were processing words that were later remembered than when they processed words that were not remembered.

Source: From "Building Memories: Remembering and Forgetting of Verbal Experiences as Predicted by Brain Activity," by A. D. Wagner et al., *Science, 281*, pp. 1188–1191. © 1998 American Association for the Advancement of Science. Reprinted by permission from AAAS.

Table 4.1
TABLE 4.1 Comparison of EEG and Imaging Techniques.

TECHNIQUE	DESCRIPTION	TIME	SPATIAL (MM)
EEG	Sums the electrical activity of neurons between two electrodes; detects fast-changing brain activity but is poor at localizing it	1 ms	10–15
CT	Forms 3-D image of brain by combining X-rays of cross sections of brain; images structure and damage	<1 ms	0.2–0.5
MRI	Measures variations in hydrogen concentrations in brain tissue; images structure and damage	3–5 s	1–1.5
PET	Produces image by emissions from injected substances that have been made radioactive; tracks changing activity, detects receptors, etc.	30 s	2–3
fMRI	Detects increases in localized blood flow and oxygen usage during neural activity; tracks changing activity	1 s	1–2

Brain imaging has been referred to as "the predominant technique in behavioral and cognitive neuroscience" (Friston, 2009, p. 399). That said, you will not be surprised to see many examples of its use throughout this text—though none will be as unusual as the one in A Further Look. However, some investigators are urging caution in interpreting results; their focus has been mostly on fMRI, but their criticisms apply more broadly. For one thing, comparison of fMRI data with data from electrode recording in monkeys showed that fMRI misses a great deal of information; this is

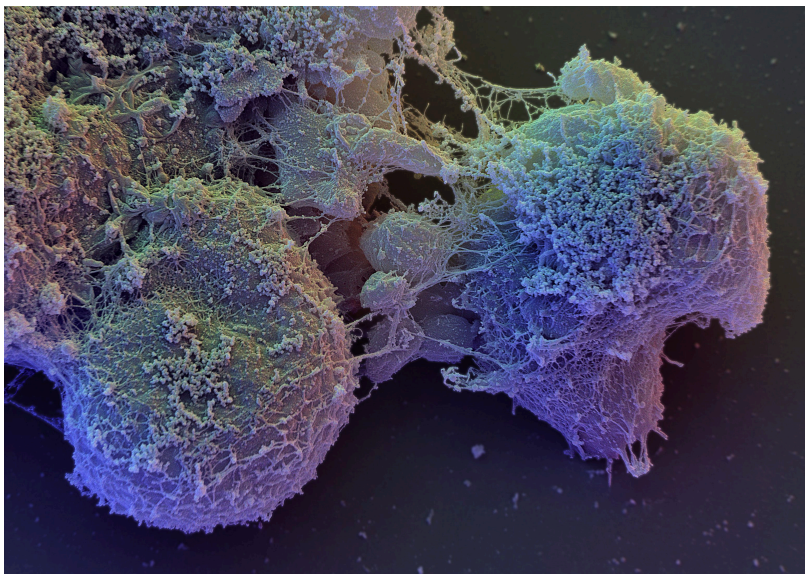
due to its lower sensitivity as well as to chance factors, such as the distance of the neurons from a blood vessel (Logothetis, 2002). A related problem is that test-retest reliability is often low. For example, when researchers showed volunteers pictures of fearful faces, correlations of amygdala activity in sessions 2 weeks apart ranged from .4 to .7 (on a scale of 0 to 1), indicating a disappointing level of consistency (Johnstone et al., 2005). (We discuss the meaning of correlations in more detail in the next section.)

A Further Look:

Scanning King Tut

In January 2005, King Tutankhamun, pharaoh of Egypt 3,000 years ago, was removed from his tomb in the Valley of the Kings for the first time in almost 80 years. The trip was a short one, to a nearby van where his mummified body was subjected to a CT scan to determine whether Tut's death at the age of 19 might have resulted from murderous intrigue within the royal family.

An X-ray conducted in the tomb 30 years earlier had found pieces of his skull inside the cranium, adding to the murder theory. But if Tut had died from a blow to the head, the bone fragments would have been caught up in the embalming material. Instead, the scan showed them lodged between the skull and the now solidified embalming fluid. More likely the archaeologist Howard Carter, who discovered Tut's tomb in 1922, damaged the skull while prying away the golden mask that was stuck to the skull by solidified resins. The scans also found no mineral deposits in the bone, which some poisons would leave behind, though other poisons could not be ruled out. The most promising evidence was that one leg had been broken, within days of his death, judging by the lack of healing. The break was severe enough to cause an open wound, so King Tut's death could have been caused by an infection. A study by an interdisciplinary research team suggested that Tut's overall health was already a liability. By combining CT scans with genetic evidence from his and some of his relatives' mummies, they concluded that he may have had multiple disorders, including a weakened immune system, and that he probably needed the numerous ornamental canes left in his tomb to walk (Hawass, 2010).



Top: Egypt's Vice Minister of Culture Zahi Hawass (center) and technicians ready Tut's mummy for scanning. Bottom: A resulting scan of Tut's head.

Kenneth Garrett / DanitaDelimont.com / Alamy Stock Photo

Kenneth Garrett / DanitaDelimont.com / Alamy Stock Photo

Perhaps more important, some researchers have been criticized for the way they select their data. Ideally, researchers should decide in advance to obtain data from a specific area, such as the amygdala, but often researchers do not have enough information to make this selection beforehand and therefore go "data snooping," scanning the entire brain. Then they divide the scan into tiny cube-shaped areas called voxels and determine which voxels' activity is correlated with performance on a task or with a characteristic of the subjects. This involves calculating literally thousands of correlations; if you have even a basic understanding of probability, you know that this procedure guarantees finding several voxels whose activity correlates with the dependent variable even when no relationship exists. Thus, to ensure reliability of the results, good researchers use a statistical correction for multiple comparisons or, even better, repeat the experiment to focus only on those areas to rule out the possibility that the original correlations occurred by chance.

However, researchers sometimes choose the easier approach of simply reporting the correlations they found in that one session. In an analysis of 53 studies that reported correlations of fMRI activity with social or emotional measures (such as distress from social rejection), more than half used the flawed nonindependent approach, and they accounted almost entirely for the highest correlations (Vul, Harris, Winkielman, & Pashler, 2009; see also the similar results of Kriegeskorte, Simmons, Bellgowan, & Baker, 2009). Nikos Logothetis has warned that erroneous claims of brain areas specialized for everything from empathy to neuroticism are leading to a phrenology that is even more dangerous than the 19th-century variety because it is cloaked in the respectability of brain imaging (Spinney, 2002).

Still, these problems do not undermine the potential of imaging studies for understanding behavior. The fact that five people won Nobel Prizes for their work in developing scanning technology indicates the importance of imaging techniques, and you can be sure that many important future developments in neuroscience will depend on brain imaging, just as they have for the past 20 years.

A deficiency of all these technologies is that they show what the brain is doing at the current time. To understand many brain processes and disorders such as schizophrenia, we also need to watch the brain as it develops. A Further Look describes an important step in that direction.

A Further Look:

Growing a Model Brain From Stem Cells

In spite of all our capabilities for scanning, probing, and recording, our ability to study the living human brain is limited by the fragility of the brain itself. Researchers have been able to simulate some limited aspects of brain functioning by culturing thin slices of neural tissue in a dish. But now scientists have learned to induce stem cells to develop into brain organoids, small three-dimensional structures that have many characteristics of the human brain (Amin & Paşca, 2018; H. Wang, 2018). These organoids can be limited to a part of the brain, such as the hypothalamus, hippocampus, forebrain, cerebellum, or cortex, or they may simulate the entire brain, with identifiable hindbrain, midbrain, forebrain, and even retinal tissues. These model brains can be manipulated in all the ways we would a real human brain; we can study normal development and functioning, or we can insert genes or obtain the stem cells from individuals with brain disorders to study the development and mechanisms of disorders such as lissencephaly (see Chapter 3) and Alzheimer's disease.

For example, Jessica Mariani and her colleagues (2015) at Yale University used this strategy in an attempt to learn why autism develops in some individuals without a clear genetic cause. To do this, they focused on a subtype of autism in which individuals have slightly enlarged heads, which affects about 20% of those with autism. They cultured stem cells from these autistic individuals to grow into organoids and compared them with organoids grown from non-autistic biological relatives. The scientists observed that after about a month of development, the organoids grown from autistic individuals were overproducing GABA-releasing neurons, due to excess activity of the *FOXG1* gene. This was the first clear identification of a neural mechanism that leads to the development of autism. Although there are still many hurdles ahead, having a cellular target during development may lead to earlier identification of factors that could result in developmental disorders such as autism.

Investigating Heredity

We looked at the interplay of heredity and environment in shaping behavior in Chapter 1. Now we need to understand some of the techniques scientists use to do genetic research. The idea that behavior can be inherited is an ancient one, but most of the methods for genetic research were introduced or came into maturity in the past three or four decades. Until then, the work was not much more sophisticated than observing that a characteristic tended to be shared within a family.

Genetic Similarities: The Correlational Approach

In a **family study**, which determines how strongly a characteristic is shared among relatives, we would find that intelligent parents usually have intelligent children. However, as one researcher put it, "cake recipes run in families, but not because of genes" (Goodwin, 1986, p. 3). This is a good example of the problem with correlational research. People who have similar genes often share a similar environment, so the effects of heredity are confounded with the effects of environment. Still, the fact that family members are similar in a characteristic tells researchers that it would be worthwhile to pursue more complicated and costly research strategies. We will look at ways to reduce the confounding of heredity with environment, but first we need a way to quantify the results.

Quantification is a simple matter for characteristics that can be treated as present or absent, such as schizophrenia. We can say, for instance, that the rate of schizophrenia is about 1% in the general population but increases to around 13% among the offspring of a schizophrenic parent (Gottesman, 1991). For variables that are measured on a numerical scale, such as height and IQ (intelligence quotient, one measure of intelligence), we express the relationship with a statistic called the *correlation coefficient*. **Correlation** is the degree of relationship between two

variables, measured on a scale between 0.0 and ±1.0. The strength of the relationship is indicated by the absolute value—how close the correlation is to *either* 1.0 or −1.0. A positive correlation means that when one variable is high, the other tends to be high as well. For example, the correlation between IQs of family members is positive: The average across studies between parents and offspring is about .42, and for brothers and sisters, it is about .47 (T. J. Bouchard & McGue, 1981). A negative correlation (<0) indicates the opposite tendency—when one value is high, the other tends to be low—not that the relationship is weaker. Now we can consider how to separate the effects of heredity from those of the environment.

An **adoption study**, which contrasts the similarity between adopted children and their biological parents with their similarity to their adoptive parents, eliminates much of the confounding of heredity and environment that occurs in family studies. This kind of study is often called a *natural experiment*, but it lacks the control of a real experiment because we do not manipulate the adoption variable. As a result, environmental confounding can still occur. For example, families that must be split up by adoption may differ from the control families in important ways. Additional confounding occurs because children are often adopted into similar family environments and because adoption is frequently delayed until after critical developmental periods have passed. Nevertheless, the technique has yielded extremely valuable information, such as the fact that rearing children apart from their biological parents results in a drop in the correlation between their IQs from .42 to about .22 (T. J. Bouchard & McGue, 1981). The drop in correlation indicates a substantial influence of environment; the remaining correlation indicates genetic influence.

? How are adoption and twin studies superior to family studies?

An environmental confound that adoption studies don't control is the prenatal environment, which can bring about long-term alterations in nervous system functioning. Animal researchers get around this problem by c*ross-fostering*, implanting a fetus or an egg into another female. Of course, this strategy is unavailable in human research, or at least it was until *in vitro* fertilization became so widespread. British researchers examined the medical records of 800 children conceived by in vitro fertilization; in one fourth of the cases, the egg or embryo was donated by another woman, so the offspring was unrelated to the mother. With this strategy, the researchers were able to conclude that the low birth weight previously observed in babies whose mothers smoked during pregnancy is environmental, whereas antisocial behavior (tantrums, fighting, lying, etc.) in children of smoking mothers has a genetic origin (F. Rice et al., 2009).

Twin studies assess how similar twins are in some characteristic; their similarity is then compared with that of nontwin siblings, or the similarity between identical twins is compared with the similarity between fraternal twins. Remember that fraternal twins are produced from two separately fertilized eggs (*dizygotic*), whereas identical twins result from a single egg that splits and develops into two individuals (*monozygotic*). Fraternal twins, like nontwin siblings, share only half their genes with each other; identical twins share 100% of their genes. Because both identical twins and fraternal twins share a common environment for the most part, a greater similarity between identical twins in a characteristic is probably due to their greater genetic similarity. Investigations of intelligence provide particularly good examples of the value of twin studies. For example, the correlation between fraternal twins' IQs is about .60, and for identical twins, it increases to around .86 (T. J. Bouchard & McGue, 1981). (Of course, we have to select fraternal pairs that are of the same sex, because identical twins are of the same sex.) Criticisms of twin studies include the possibility that identical twins might be treated more similarly than fraternal twins, and the fact that they usually share the same placenta and sometimes the amniotic sac makes their prenatal environment more similar.

A useful measure for identifying genetic influence is **concordance rate**, the frequency with which relatives are alike in a characteristic. An example of this measure is that when one fraternal twin is schizophrenic, the second twin will also be diagnosed with schizophrenia about 17% of the time; in identical twins, this measure almost triples, to 48% (Figure 4.19; Gottesman, 1991). But because the correlation falls short of a perfect 1.0, even the identical twin of a person with schizophrenia

escapes schizophrenia about half of the time; for the same reason, identical twins will rarely have exactly the same IQ. The incomplete influence of heredity means that environmental effects are also operating. Family, adoption, and twin studies are compared in Table 4.2.

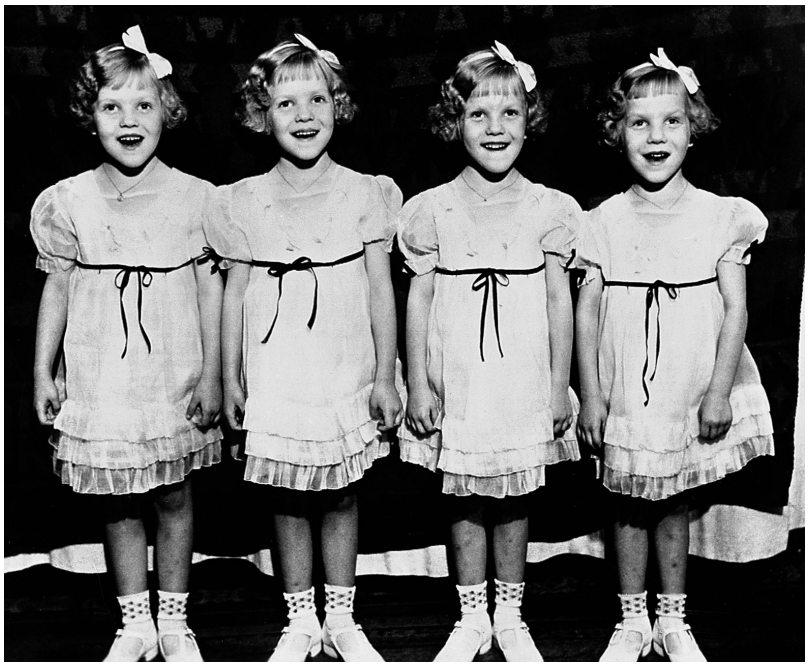


Figure 4.19 The Genain Quadruplets.
Identical quadruplets, the sisters all became schizophrenic later in life. The chances of any four unrelated individuals all being schizophrenic is 1 in 100 million. The name *Genain* is a nickname derived from the Greek word meaning “dreadful gene.”

ASSOCIATED PRESS

Table 4.2
TABLE 4.2 Comparison of Relationship Studies.

FAMILY STUDY	ADOPTION STUDY	TWIN STUDY
• Indicates how strongly a characteristic is shared among relatives • Can show that a characteristic follows family lines • Confounds heredity and environment	• Compares adopted children with their adoptive parents and their biological parents • Susceptible to confounding because the adoption variable is not manipulated	• Compares similarity of twins with that of nontwin siblings, or similarity of identical twins with similarity of fraternal twins • Allows comparison of two levels of genetic similarity

Genetic Engineering: The Experimental Approach

Although adoption and twin studies reduce confounding, they still share some of the disadvantages of correlational studies. **Genetic engineering** involves manipulation of the organism’s genes or their functioning. Studies using this technology qualify as experiments. At present, genetic engineering is employed mostly with mice, because their genetic makeup is well known and their embryos are more successfully manipulated.

? What advantage does genetic engineering have over adoption and twin studies?

An obvious way to find out what a gene does is to disable it and see what effect this has on the animal. In the **knockout technique**, a nonfunctioning mutation is introduced into the isolated gene, and the altered gene is transferred into embryos. Subsequent mating of the resulting animals is required to produce animals that are homozygous for the gene. **Knockdown technique** involves silencing a gene by interfering with its expression. One way is to use **antisense RNA**, a strand of RNA that is complementary to messenger RNA, which binds to the mRNA and blocks the gene's expression (Figure 4.20). Antisense RNA occurs naturally and regulates gene expression in both plants and animals; artificial antisense RNA has shown therapeutic potential in treating cancers and viruses such as HIV, hepatitis B, and influenza (Billioud et al., 2016; J. Xu, Zhang, & Zhang, 2018).

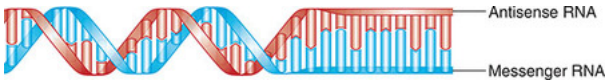


Figure 4.20 Antisense RNA.
Antisense RNA is a strand of RNA that is complementary to a particular messenger RNA. The two will dock with each other, which disables the messenger RNA and halts production of its protein. The researcher observes differences in the animal to determine the gene's function.

In **gene transfer**, a gene from another organism is inserted into the recipient's cells. An important research tool is the *transgenic animal*, created by inserting the gene into the developing embryo. Again, mating of these animals is required to integrate the gene into all the cells. Researchers observe the effects in recipient animals to determine the transferred gene's function. One fascinating new way to investigate the connections in the nervous system is *Brainbow*, which is described in A Further Look.

A Further Look:

The Brainbow Connection

Genetic engineering has enabled researchers to develop a major new technique for labeling and visualizing neurons, appropriately called *Brainbow*. Genes that produce phosphorescent proteins in three or four colors are inserted into an animal's genome; these combine in random combinations in neurons, labeling individual cells in as many as 100 different hues. Using light microscopy, the researcher is able to trace a neuron's path and view and photograph the connectome.

Gene therapy, the treatment of disorders by manipulating genes, does not allow the luxury of multiple generations to distribute the gene to all the cells. Typically the gene is carried into the individual by a vector, most often a disabled virus, which is injected directly into the diseased tissue or into the bloodstream near the target organ. Alternatively, the possibility of an immune response can be reduced by inserting the genes into cells removed from the patient's body, which are then returned to the patient. Some diseases that are treatable with gene therapy or are showing promise include spinal muscular dystrophy, SCID (the "bubble boy disease" discussed earlier), and hemophilia (Bassett, 2019).

An adaptation of a strategy that bacteria use as a defense against an invading virus is enabling researchers to manipulate genes with much greater accuracy and efficiency. When viruses invade bacteria, the bacteria retain fragments of the virus's DNA known as *CRISPR* (for *clustered regularly interspaced short palindromic repeats*). The bacteria then use these snippets to identify the DNA of similar new viruses; an enzyme (CRISPR-associated protein 9, or Cas-9) then cuts the virus's DNA, disabling the virus. In the adaptation, the researcher creates a small strand of RNA, which binds to the Cas-9 enzyme; when the enzyme identifies a similar stretch of DNA, it cuts the ends of the DNA. The cell then patches the break or inserts replacement DNA, which is also carried by the Cas enzyme. Thus, the technique can be used to delete or disable a defective gene or to insert a beneficial gene at the location.

In spite of some disastrous setbacks along the way, genetic engineering is becoming a therapeutic reality. Gene therapy for a type of SCID has been approved by the European Commission after trial patients had a 100% survival rate, some as long as 13 years following treatment (Nield, 2016). A new gene insertion procedure has halted the brain myelin–destroying disease adrenoleukodystrophy (ALD) in all but 1 of 17 boys (Kaiser, 2016). (A family's struggle to save their son from ALD was the subject of the 1992 movie *Lorenzo's Oil*.) In 2016, a Chinese group performed the first officially sanctioned gene editing with a human using the powerful CRISPR technique (Cyranoski, 2016). CRISPR is faster, cheaper, and more precise than previous gene-editing techniques, so we will be hearing a great deal more about it in the future. Gene manipulation holds a great deal of promise for research and the treatment of disease, but the ability to manipulate our genome carries tremendous risks and raises important ethical questions, as we will see in the next section.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- Organize your knowledge: Make a table of the staining and labeling techniques and their functions.
- What different ways could be used to determine the function of a part of the brain?
- Name three procedures that can be used to identify receptors.
- What are the advantages and disadvantages of experimental studies and correlational studies?
- Describe the different genetic manipulation strategies discussed in this chapter.

RESEARCH ETHICS

As important a topic as research ethics is, it usually gets pushed into the background by the excitement of scientific accomplishments and therapeutic promise. To place ethics at the forefront where it belongs, the major scientific and medical organizations have adopted strict guidelines for conducting research, for the treatment of subjects, and for communicating the results of research (see, for example, American Psychological Association, 2017; National Institutes of Health, 2015; Society for Neuroscience, n.d.).

? What are the main issues in research integrity?

Plagiarism and Fabrication

The success of research in answering questions and solving problems depends not only on the researchers' skill in designing studies and collecting data but also on their accuracy and integrity in communicating results. Unfortunately, research is sometimes misrepresented intentionally; the two cardinal sins of research are plagiarism and the fabrication of data.

Plagiarism is the theft of another's work or ideas. Plagiarism denies individuals the credit they deserve and erodes trust among the research community. The infraction may be as simple as failing to give appropriate credit through citations and references (like those you see throughout this text), but occasionally a researcher literally steals another's work. In a recent high-profile case, for example, German education minister Annette Schavan resigned after the University of Düsseldorf revoked her PhD due to plagiarism. According to the university, large parts of her 1980 dissertation had been

lifted from other sources with only slight paraphrasing and without crediting those sources (“German Education Minister Quits,” 2013).

Fabrication, or faking, of results is more serious than plagiarism because it introduces erroneous information into the body of scientific knowledge. As a result, the pursuit of false leads by others consumes scarce resources and sidetracks researchers from more fruitful lines of research. More important, fabrication in clinical research can slow therapeutic progress and harm lives. In 1998, Andrew Wakefield published a study implicating a preservative in some vaccines as a cause of autism. No one could replicate the results, and later investigation revealed numerous instances of data fabrication and misrepresentation in the research (Deer, 2011). The article was retracted, and Wakefield lost his medical license, but the repercussions continue today. Many parents have become suspicious of vaccines and are failing to have their children immunized. As one result, although measles was declared eliminated from the United States in 2000, more than 2,400 people were infected between 2010 and mid-2019 (Centers for Disease Control and Prevention, 2019), and several locales such as New York City have declared public health emergencies.

Cases of this magnitude are very rare, but 2% of researchers admit in surveys that they have falsified research at least once in their career (Fanelli, 2009). That amounts to a large volume of erroneous data potentially being used by others to develop theories, devise therapies, and guide further research. Scientific journals, universities, and other authorities take the issue seriously. The U.S. government, which funds 44% of basic research (Mervis, 2017), requires grant recipients to receive training in research ethics (R. Dalton, 2017), funds studies on research integrity, and discourages financial conflicts of interest in biomedical research (“Federal Financial Conflict of Interest Rules…,” 2014).

Recently, the government sued Duke University, alleging that one of its biologists—coauthor of several papers that have now been retracted from publication—submitted fraudulent data in 60 grant reports and funding applications to U.S. agencies. Duke agreed to settle the lawsuit by paying $112.5 million and taking steps to improve the quality and integrity of its research (Science News Staff, 2019).

Protecting the Welfare of Research Participants

All the scientific disciplines that use live subjects in their research have adopted strict codes for the humane treatment of both humans and animals. The specifics of the treatment of human research participants and even the legitimacy of animal research are controversial, however. These are not abstract issues. As a student, you are a consumer of the knowledge that human and animal research produces, and you benefit personally from the medical and psychological advances, so you are more than just a neutral observer.

Research With Humans

In 1953, the psychologist Albert Ax performed a study that was as significant for its ethical implications as it was for its scientific results. He was attempting to determine whether all emotions result in the same general bodily arousal or each emotion produces a unique pattern of activation. To do so, he measured several physiological variables sensitive to emotional arousal, such as heart rate, breathing rate, and skin temperature, while inducing anger in the individuals at one time and fear at another. If Ax had told the research participants what would happen during the study, it would have altered their behavior, so he said he was doing a study of blood pressure.

? What are the principal ethical concerns in human research?

In the “anger” condition, the research participant was insulted by Ax’s assistant, who complained at length that the person was not a very good experimental subject. The “fear” situation was more intense. During the recordings, the individual received a mild electrical shock through the recording electrodes, while sparks jumped from

nearby equipment. The experimenter acted alarmed as he explained that there was a dangerous high-voltage short circuit. Later interviews indicated that both ruses worked. Ax (1953) reported that one participant kept pleading during the fear treatment, “Please take the wires off. Oh! Please help me.” Another said of the anger treatment, “I was just about to punch that character on the nose” (p. 435). You will find the results of Ax’s research described in Chapter 8; here we will look at the issues of informed consent and deception in relation to his study.

Occasionally, research involves some pain, discomfort, or even risk. Before proceeding with a study, current standards require the researcher to obtain the participant’s informed consent. **Informed consent** means that the individual voluntarily agrees to participate after receiving information about any risks, discomfort, or other adverse effects that might occur. However, sometimes the nature of a study requires the researcher to use **deception**, failing to tell the participants the exact purpose of the research or what will happen during the study or actively misinforming them. According to the American Psychological Association (APA), deception is acceptable only when the value of the study justifies it, alternative procedures are not available, and the individuals are correctly informed afterward. The APA’s guidelines are also clear that psychologists should not deceive participants about research that is reasonably expected to cause physical pain or severe emotional distress (American Psychological Association, 2017). Some researchers and participants’ rights advocates believe that deception is never justified. Ax’s study would probably not be permitted today, but we will see in Chapter 8 that researchers have found interesting alternatives for doing this kind of research.

But the consent factor is not always as straightforward as it seems. Does requiring students in a research methods course to participate as subjects in the laboratory exercises violate the principle of informed consent? If homeless individuals are offered a warm bed, food, and money to participate in a month-long drug study, can their consent be considered entirely voluntary? And as a sidelight to the now-famous CRISPR baby scandal (described shortly in A Further Look), a Chinese lawyer has said that the researcher’s offer to cover the cost of the mother’s fertility treatment but require repayment if the parents dropped out could be considered coercive and therefore constitute a crime (Cyranoski, 2019).

Research With Animals

Psychological and medical researchers have perhaps no more important resource than the laboratory animal. As the American Medical Association (1992) concluded, “virtually every advance in medical science in the twentieth century, from antibiotics and vaccines to anti-depressant drugs and organ transplants, has been achieved either directly or indirectly through the use of animals in laboratory experiments” (p. 11). Psychologists have used animals to investigate behavior, aging, pain, stress, and cognitive functions such as learning and perception (D. Blum, 1994; F. A. King, Yarbrough, Anderson, Gordon, & Gould, 1988; N. F. Miller, 1985). It may seem that the best participants for that purpose would be humans, but animals are useful because they live in a controlled environment and have a homogeneous history of experience, a briefer development, and a shorter life span. In addition, researchers feel that it is more ethical to use procedures that may be painful or physically or psychologically risky on other animals than on humans. As a result, in the mid-1980s, U.S. scientists were using 20 million animals per year: 90% of them were rodents, mostly mice and rats, and around 3.5% were primates, mostly monkeys and chimpanzees (U.S. Congress Office of Technology Assessment, 1986).

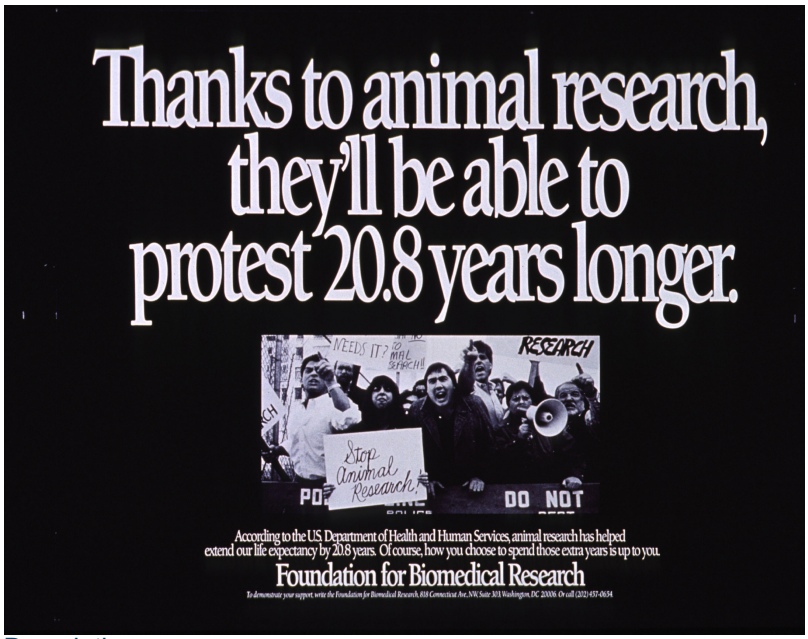
? What are the opposing views on animal research?

The preference for inflicting discomfort or danger on nonhuman animals rather than on humans is based on the assumption that the well-being of animals is less important than that of humans. Animal rights activists have called this dual ethical standard *speciesism* (H. A. Herzog, 1998), a term chosen to be intentionally similar to *racism*. Some activists work hand in hand with researchers to improve conditions for research animals; others have been more aggressive, breaking into labs, destroying equipment and records, and releasing animals (typically resulting in the animals’

death). Activists have been shifting their attacks from laboratories to the researchers themselves; since the 1990s, attacks on individuals have risen from 9% of incidents to 46% (Grimm, 2014). At the University of California at Santa Cruz, one animal researcher's home was firebombed, and another's car was burned (G. Miller, 2008). And when Italy's Ministry of Health approved research using monkeys to study blindness and then gave an animal rights group the names of the researchers, the lead investigator received death threats and is now under police protection (Abbott, 2019).

Animal research guidelines provide for humane housing of animals, attention to their health, and minimization of discomfort and stress during research. But critics point out that researchers sometimes do not live up to the standards of their professional organizations. The Behavioral Biology Center in Silver Spring, Maryland, was engaged in research that involved severing the sensory nerve in one arm of monkeys to study the reorganization that occurs in the brain. The lab's contributions drew the praise of neuroscientists and led to the design of routines for extensive exercise of an afflicted limb to help people recover from brain injuries. But in 1981, a student summer employee informed the police of what he considered to be abuse of the lab's animals, and the police carried out the first raid on a research laboratory in the United States ("A Brighter Day for Edward Taub," 1997; Orlans, 1993). The director, Edward Taub, was convicted of animal abuse because of poor postoperative care, but the conviction was overturned because the state lacked jurisdiction over federally supported scientific research. The National Institutes of Health (NIH) withdrew Taub's funding, and Congress enacted more stringent animal protection laws. In spite of the controversy, Taub received the William James Award from the American Psychological Society. However, he points out that the award was for work that is no longer permitted and that animal welfare rules enacted by Congress prevent him from taking measurements in the brain of the one remaining monkey for the length of time that would be needed.

The conflict between animal welfare and research needs is obviously not a simple issue and is strongly felt on both sides (Figure 4.21). Although psychologists and neuroscientists do not condone mistreatment of research animals, most of them argue that the distress that does occur is justified by the benefits animal research has produced. The 2000 Nobel Prize in physiology or medicine was shared by three neuroscientists: Arvid Carlsson, for his discovery of the role of dopamine as a neurotransmitter in the brain; Paul Greengard, for identifying how dopamine and related neurotransmitters produce their effect on neurons; and Eric Kandel, for his work on the molecular changes that occur in the brain during learning. The work of all three prize winners relied heavily on animal research.



Description

Figure 4.21 Animal Research Controversy.
The poster illustrates the contrasting views on animal research.

Source: Foundation of Biomedical Research.

It is unlikely that animal research will be banned, as the more extreme activists demand, but animal care and use guidelines have been tightened and outside monitoring increased, and states have passed more stringent laws. In addition, researchers have become more sensitive to the welfare of animals, adopting more humane methods of treatment and turning to tissue cultures and computer simulations in place of live animals when possible. In a survey of articles published in major biomedical journals between 1970 and 2000, the proportion of studies using animal subjects had fallen by one third, and in the studies that did use animals, the average number had decreased by half (Carlsson, Hagelin, & Hau, 2004). In response to restrictive legislation, the U.S. Environmental Protection Agency (2019) has said it will stop conducting or funding chemical safety studies on mammals by 2035. It is beginning fund research to develop alternatives, including non-mammalian species, brain organoids, artificial organs, and cell cultures. In addition, when the U.S. Fish and Wildlife Service declared the chimpanzees used in U.S. research endangered, the NIH ended all support for chimp studies and began moving the animals from laboratories to sanctuaries (Grimm, 2018b). In spite of the retirement of chimps, laboratory use of monkeys is at a record level in the United States, apparently driven by researchers studying the brain, Alzheimer's disease, HIV/AIDS, and addiction, as well as by increased funding from the NIH (Grimm, 2018a).

Human research has typically generated less controversy than the use of animals, largely because scientists are more restrained in their treatment of humans, and humans are able to refuse to participate and to bring lawsuits. The balance of concern is shifting, though, particularly as treatments move from the research lab to the clinic.

Gene Therapy

Gene therapy has enjoyed glowing press reviews because of its potential for correcting humanity's greatest handicaps and deadly diseases. But a distinct chill fell over the research in 1999, when Jesse Gelsinger, an 18-year-old patient volunteer, became the first human to die as the direct result of gene research (Lehrman, 1999;

E. Marshall, 2000). The study was using a deactivated form of adenovirus, which causes the common cold, to transport a gene into the liver in an experimental attempt to correct a genetic liver enzyme deficiency. Gelsinger developed an immune reaction to the adenovirus, which resulted in his death.

? What are the problems with gene research and gene therapy?

The Food and Drug Administration (FDA), which was overseeing the study, reprimanded the researchers for not consulting with the FDA when most of the patients developed mild adverse reactions and for not informing the research participants that two monkeys had died in an earlier study after receiving much larger doses of adenovirus ("U.S. Government Shuts Down Pennsylvania Gene Therapy Trials," 2000). The university was assessed a $1 million fine, and the three principal investigators had restrictions placed on their human research until 2010 (Check, 2004). The case slowed gene therapy research across the country, but a positive outcome is that it has led to stricter supervision of human studies.

Besides the safety issue, there are significant concerns about how this technology will be used. The most important concern is that gene manipulation could affect the reproductive cells and change the genome of nonconsenting future generations. A gene-editing summit called by CRISPR co-discoverer Jennifer Doudna and 17 other scientists, the Alliance for Regenerative Medicine, and several U.S. government agencies has urged researchers to forgo gene editing that could modify the genetic line until its safety and ethical implications can be determined (Alliance for Regenerative Medicine, 2015a, 2015b).

Another concern is that as gene editing becomes more common, there will be mounting pressure to go beyond correcting disabilities and disease to enhancing the beauty, brawn, and intelligence of individuals and their offspring. This is an ethical issue in its own right, but many also fear that because gene therapy is very expensive, it is likely to increase inequalities further between the haves and have-nots in our society. The science fiction movie *Gattaca* (whose title is a play on the four letters of the genetic code) depicts a society in which privilege and opportunity are reserved for genetically enhanced "superior" individuals. Fortunately, the U.S. Congress wisely set aside 5% of the Human Genome Project budget to fund the study of the ethical, legal, and social implications of genetic research (Jeffords & Daschle, 2001).

In the meantime, both Chinese and U.S. scientists have used the CRISPR technique to modify genes in single-cell human embryos (Liang et al., 2015; Ma et al., 2017). The embryos were not allowed to grow beyond a few cells; editing embryos for implantation in the mother is banned in most countries. An international committee convened by the U.S. National Academy of Sciences and the National Academy of Medicine concluded that editing the DNA of a human embryo for implanting "might" be permitted in the future but only following much more research and only when it is the last reasonable option for producing a healthy child (National Academy of Sciences and National Academy of Medicine, 2017). Chinese scientists have now demonstrated that the entire genome of embryos can be sequenced from the mother's blood (F. Chen et al., 2017), which will increase the pressure to use gene editing to reduce health risks in unborn children and improve their physical and mental performance. A Further Look reveals that the genie may already be out of the bottle.

A Further Look:

Can Gene Editing Be Regulated?

Responsible organizations throughout most of the world are opposed to genetic modification of viable human embryos, gene alteration that could be passed on to offspring, sand gene editing to improve capabilities. For example, the World Anti-Doping Agency, which sets standards for more than 600 sports organizations, including the International Olympic Committee, now bans gene editing and alteration

of gene expression in its athletes (Le Page, 2017). But official pronouncements don't always curtail the actions of individuals. Biochemist Joshua Zayner injected himself with DNA edited to remove the gene for myostatin, which regulates muscle growth, with the intent of boosting his strength. Now he is selling a kit with instructions for using the CRISPR gene-editing technique, so that the user can do the same thing (Pearlman, 2017).

In Chapter 1, we described an attempt to edit the genomes of two female embryos by using the CRISPR gene-editing technique. Though the motivation was commendable—the father was HIV positive, and the gene replacement was intended to confer HIV immunity—the researcher proceeded without obtaining ethical approval or conducting safety trials (Cyranoski, 2019; Davies, 2019). Gene editing can have unexpected consequences; in this case, the CCR5 gene influences intelligence and susceptibility to various infections, including the West Nile Virus (Cyranoski; Regalado, 2019). In addition, a recent study found that people who have two of the HIV-resistant alleles are 21% less likely to reach the age of 76 (Wei & Nielsen, 2019).

Stem Cell Therapy

? What are the promises and problems associated with stem cell therapy?

You learned in Chapter 3 that embryonic stem cells are undifferentiated cells that are pluripotent, with the potential for developing into any other body cell. Although most applications of stem cell therapy are still experimental, clinical trials have shown improvement with several conditions, including traumatic brain injury (Weston & Sun, 2018), spinal cord injury (Gazdic et al., 2018), stroke (Marei et al., 2018), macular degeneration (Kashani et al., 2018), and multiple sclerosis (Atkins et al., 2016).

So if stem cell therapy holds such wonderful potential, why is it being discussed under the topic of *ethics*? One reason is the possibility that scientists could create human embryos for research purposes, which is repugnant for some people on moral grounds. More important, extracting stem cells from an embryo destroys the embryo, so right-to-life advocates oppose using this source, even though most of the embryos are "left over" from fertility treatments and would otherwise be discarded (Figure 4.22). Stem cell research was stymied for years in the United States by the George W. Bush administration's refusal to fund research on stem cell lines derived from embryos after August 2001; however, the earlier lines were too contaminated for human use (M. J. Martin, Muotri, Gage, & Varki, 2005). This policy was reversed in 2009 by President Barack Obama, and after a 3-year court battle, a federal appeals court ruled that government funding of research with human embryonic stem cells does not violate existing U.S. law (Kaiser, 2012). Research with embryonic stem cells is still controversial in the United States, and future government leaders may slow (or stop) stem cell research; in the European Union's 27 member nations, views differ as much as they do in the United States (Drumi, 2009). Because of the controversy and the limited availability of embryonic stem cells, researchers have been forced to find other sources. Adult stem cells normally can mature only into the kind of cells where they are located, areas that require frequent cell replacement, such as the bone marrow and skin. Fortunately, these can be turned into embryonic-like *induced pluripotent stem cells* by increasing the expression of their genes.

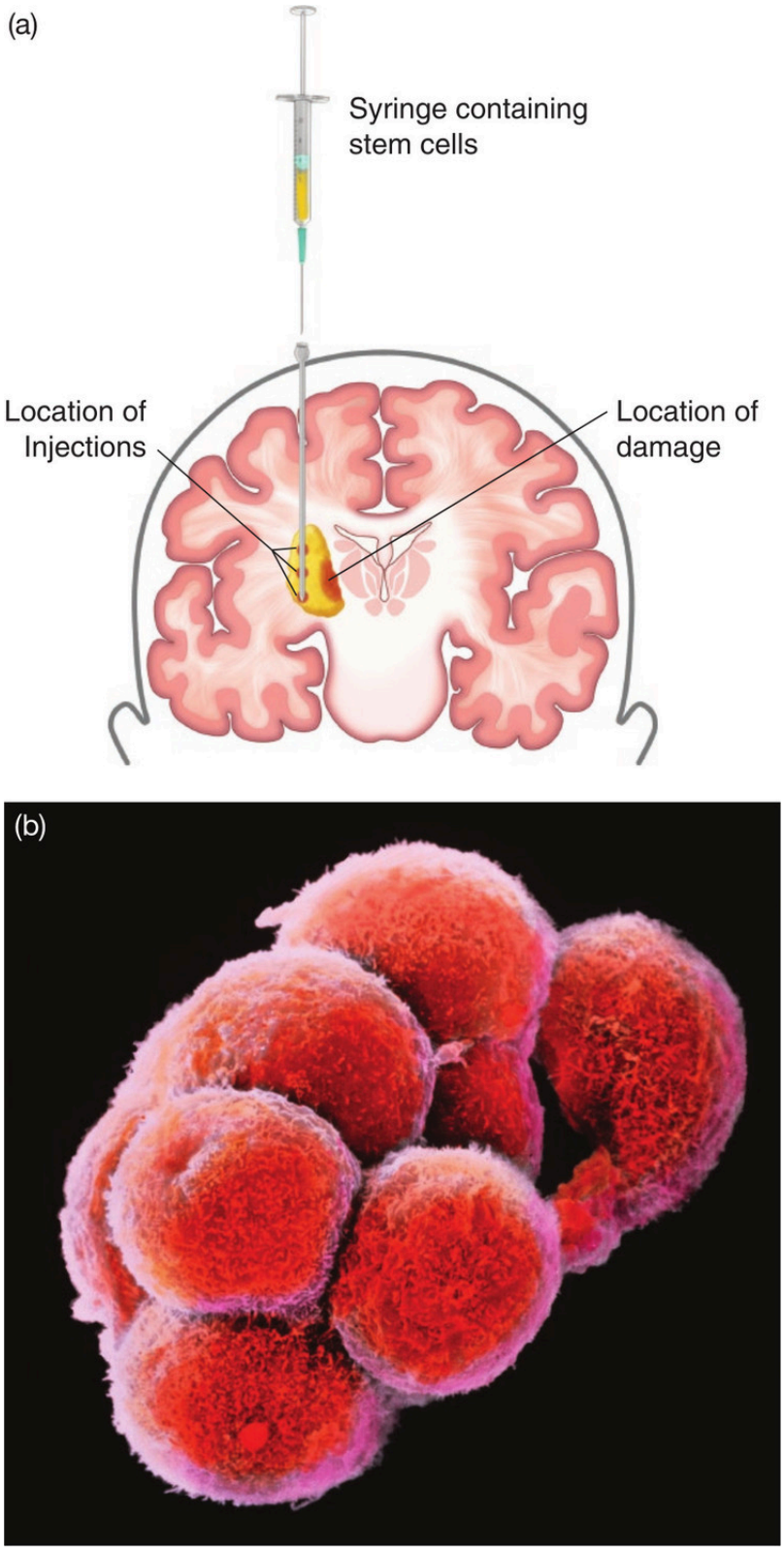


Figure 4.22 Injecting Cells Into a Damaged Brain.
Although the procedure (a) is promising, it is controversial because of where the cells (b) come from, which is usually human embryos.

Sources: (a) From Coon, *Introduction to Psychology*, 9E. © 2001 South-Western, a part of Cengage Learning, Inc. Reproduced by permission. (b) © PROFESSORS P.M. MOTTA and J. VAN BLERKOM/Science Source.

Another reason for including this topic in a discussion of ethics is that the only stem cell therapies approved by the FDA use cells from bone marrow or cord blood to treat cancers of the blood and bone marrow. Yet numerous clinics offer treatments for a wide range of medical problems, often making unfounded and misleading claims about their effectiveness. In several cases, this has resulted in serious adverse effects, including blindness, kidney failure, and partial paralysis (G. Bauer, Elsallab, & Abou-El-Enein, 2018; M. Levy, 2019).

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- What are the effects of dishonesty in research?
- How do researchers justify their use of animals in research?
- What do you think about genetically modifying a nonviable embryo to learn how the gene causes a deadly disease? What about modifying an embryo to prevent a severe mental deficiency, before implanting it in the mother? What about modifying an embryo to increase the child's intelligence or athletic ability?
- Why is there an ethical issue with human stem cell research? How might it be resolved?

IN PERSPECTIVE

Early progress in psychology and in behavioral neuroscience relied on the wit and perspiration of the pioneering researchers. Now researchers are aided by sophisticated equipment and methods that are escalating discovery at an unprecedented pace and taking research into areas that were barely conceivable a few decades ago.

Knowledge is power, and with power comes responsibility. For the scientists who study behavior, that responsibility is to the humans and animals that provide the source of our knowledge and to the people who may be healed or harmed by the new treatments resulting from research.

Chapter Summary

Science, Research, and Theory

- Researchers respect uncertainty but try to reduce it through research and the use of theory.
- Of the many research strategies at their disposal, behavioral neuroscientists favor the experimental approach because of the control it offers and the ability to determine cause and effect.
- Correlational techniques have value as well, particularly when the researcher cannot control the situation.

Research Techniques

- Staining and labeling techniques make neurons more visible, emphasize cell bodies or axons, trace pathways to or from a location, and identify active areas or specific structures such as receptors.
- Light microscopy is extremely useful, but electron microscopy reveals more detail, scanning electron microscopy adds three-dimensionality, and confocal and two-photon microscopy produce images at greater depths.
- The EEG sums the neural activity between two electrodes to assess arousal level and detect damage and some brain disorders. Event-related potentials measure averaged responses to brief stimuli.
- Brain functioning can be studied by observation of brain-damaged individuals, electrical and chemical stimulation (using stereotaxic techniques), destruction of neural tissue (ablation and lesioning), and microdialysis of brain chemicals.
- Brain imaging using CT and MRI depicts structure, for example, to assess damage, whereas PET and fMRI are capable of measuring activity.
- Family studies, adoption studies, and twin studies are correlational strategies for investigating heredity. Family studies determine whether a characteristic runs in families, while adoption studies assess whether adopted children are more like their adoptive parents or their biological parents in a characteristic. Twin studies contrast the similarity of fraternal twins with the similarity of identical twins.
- Genetic engineering includes gene transfer and gene-disabling techniques (knockout and knockdown, for example, using asNA). Although experimental, it is already showing therapeutic promise.

Research Ethics

- A major concern in behavioral neuroscience is maintaining the integrity of research; plagiarism and fabrication of data are particularly serious infractions.
- Both the public and the scientific community are increasingly concerned about protecting the welfare of humans and animals in research. The various disciplines have standards for subject welfare, but the need for more monitoring and training is evident.

- Stem cell technology is promising for treating brain and spinal cord damage and a variety of diseases, but it is controversial because obtaining stem cells often involves destroying embryos. Gene therapy also holds much promise, but it has dangers and could be abused.

Study Resources

For Further Thought

- Pay close attention as you read through this text, and you will notice that human studies are more likely than animal studies to be correlational. Why do you think this is so?
- Genetic engineering is mostly a research technique now. What practical uses can you imagine in the future?
- In the chapter, we asked whether it is unreasonable coercion to require students to participate in research or to offer food, shelter, and money to homeless individuals to participate in research. What do you think? Why?
- Do you think the rights of humans and animals are adequately protected in research? Why or why not? What do you think would be the effect of eliminating the use of animal subjects on the progress of research?

Test Your Understanding

1. Describe the imaging techniques, including method, uses, and advantages and disadvantages.
2. Discuss the relative merits of experimental and correlational research, using family, twin, and adoption studies versus genetic engineering as the example.
3. Discuss the conflicts between research needs and animal rights.
4. In spite of their promise, stem cell research and gene therapy are controversial. Why?

Select the best answer:

1. You could best identify receptors for acetylcholine by using
    1. Golgi stain.
    2. Nissl stain.
    3. immunocytochemistry.
    4. electron microscopy.
2. If you needed to measure brain activity that changes in less than 1 s, your best choice would be
    1. EEG.
    2. CT.
    3. MRI.
    4. PET.
3. Your study calls for daily measurement of activity changes in emotional areas of the brain. You would prefer to use
    1. CT.
    2. MRI.
    3. PET.
    4. fMRI.
4. Science is most distinguished from other disciplines by
    1. the topics it studies.
    2. the way it acquires knowledge.
    3. its precision of measurement.
    4. its reliance on naturalistic observation.
5. Experiments are considered superior to other research procedures because they

1. involve control over the variable of interest.
2. permit control of variables not of interest.
3. permit cause-and-effect conclusions.
4. All of the above
5. None of the above

6. A theory
    1. is the first step in research.
    2. is the final stage of research.
    3. generates further research.
    4. is an opinion widely accepted among researchers.
7. The best way to assess the relative contributions of heredity and environment would be to compare the similarity in behavior of
    1. fraternal versus identical twins.
    2. relatives versus nonrelatives.
    3. siblings reared together versus those reared apart.
    4. fraternal versus identical twins, half of whom have been adopted out.
8. The most sensitive way to determine whether a particular gene produces a particular behavior would be to
    1. compare the behavior in identical and fraternal twins.
    2. compare the behavior in people with and without the gene.
    3. use genetic engineering to manipulate the gene and note the behavior change.
    4. find out whether people with the behavior have the gene more often than people without the behavior.
9. Antisense RNA technology involves
    1. inserting a gene into the subject's cells.
    2. interfering with protein construction controlled by the gene.
    3. introducing a nonfunctioning mutation into the subject's genes.
    4. All of the above
10. The most popular research animals among the following are
    1. rats.
    2. pigeons.
    3. monkeys.
    4. chimpanzees.
11. Speciesism refers to the belief that
    1. humans are better research subjects than animals.
    2. it is more ethical to do risky experiments on lower animals than on humans.
    3. studying animals permits more experimental control.
    4. All of the above
    5. None of the above
12. The CRISPR technique is controversial because
    1. it more effectively produces potentially unethical genetic alterations.
    2. several research subjects have died.
    3. it relies on human fetuses.
    4. All of the above

Answers:

1. c, 2. a, 3. d, 4. b, 5. d, 6. c, 7. d, 8. c, 9. b, 10. a, 11. b, 12. a.

For Further Reading

1. "The Past, Present and Future of Light-Gated Ion Channels and Optogenetics," by Sheena Josselyn (*eLife*, October 22, 2018, available at https://elifesciences.org/articles/42367), reviews recent strategies and applications of optogenetics.
2. "Cluster Failure: fMRI False Positives Revisited" (*Discover*, July 22, 2018, available at discovermagazine.com) discusses papers by one of fMRI's most ardent critics and why new methods for analyzing the data have been devised.
3. "Methods for Creating Transgenic Primates," by Christine M. Scaduto (*Lab Animal*, 2016, *45*, 291–292, available at www.nature.com/articles/laban.1068), describes some of the advances in the field while illustrating one of the arguments for the use of animals in research.

4. Opposing views of several writers on research deception are presented in *American Psychologist*, July 1997, 746–747, and July 1998, 803–807.
5. In “20 Years of Human Pluripotent Stem Cell Research: It All Started With Five Lines” (*Cell Stem Cell*, 2018, *23*, 644–648), Tenneille Ludwig and her colleagues describe the history of stem cell research and its impact on therapy, industry, and even the economy.
6. “Selling Stem Cells in the USA: Assessing the Direct-to-Consumer Industry,” by Leigh Turner and Paul Knoepfler (*Cell Stem Cell*, 2016, *19*, 154–157), describes the proliferation of clinics offering unauthorized and unproven treatments for dozens of diseases.

Key Terms

ablation 105

adoption study 112

antisense RNA 114

autoradiography 95

computed tomography (CT) 106

concordance rate 113

correlation 112

correlational study 93

deception 117

diffusion tensor imaging (DTI) 107

electroencephalogram (EEG) 100

event-related potential 101

experimental study 93

fabrication 116

family study 111

functional magnetic resonance imaging (fMRI) 108

gene therapy 115

genetic engineering 114

gene transfer 114

Golgi stain 95

immunocytochemistry 97

informed consent 117

in situ hybridization 98

knockdown technique 114

knockout technique 114

lesioning 105

magnetic resonance imaging (MRI) 107

messenger ribonucleic acid (mRNA) 98

myelin stain 95

Nissl stain 95

plagiarism 116

positron emission tomography (PET) 107

scanning electron microscope 99

stereotaxic instrument 102

theory 93

transcranial magnetic stimulation (TMS) 105

transmission electron microscope 98

twin studies 112

Descriptions of Images and Figures

Back to Figure

1. Correlational studies: The two variables are A. Observed frontal lobe impairment and B. Violent criminal behavior. A causes B and B causes A. A third variable, drug use or physical abuse, causes both A and B.
2. Experimental behavior: Induced frontal lobe impairment I V causes aggressive behavior D V. Confounding variables do not affect D V. Because the experimenter induces the brain impairment, it is not confounded with drug use or physical abuse.

Back to Figure

1. A micrograph shows neurons stained dark.
2. A cross section of the brain shows regions with white matter and neural pathways stained blue.
3. A cross section of the brain shows dark spots, corresponding to cell bodies, along the gyri and sulcus.

Back to image

The first image is a photo that shows the brain of a mouse placed on a block text. The text under the mouse’s brain is not visible.

The second image is a photo that shows the translucent brain of the mouse after clarification. The brain is placed on a block of text that reads, The brain is a world consisting of a number of unexplored continents and great stretches of unknown territory.

The third image shows a multicolored, stained, and curved structure of the hippocampus within a box. The neurons are in green, the connecting interneurons are in red, and the glia are in blue.

Back to Figure

1. The illustration shows a network of electrodes applied on the scalp of a man.

2. The graph shows time along the horizontal axis and voltage along the vertical axis. The fluctuation pattern during different levels of consciousness are as follows.

    - Awake: Low-voltage, high-frequency brain waves.
    - Drowsy: Higher-voltage, slower-frequency brain waves.
    - Deep, dreamless sleep: High-voltage, low-frequency brain waves

Back to Figure

1. The horizontal axis of the graph ranges from negative 200 to 700 milliseconds in increments of 100. A stimulus is applied at 0 milliseconds. The potential is constant at a high value till the stimulus is applied, after which the potential decreases gradually.
2. The illustration shows five rows of stimulus response during different levels of consciousness. Each row shows response to three kinds of stimulus: Language, music, and motor imagery. The response to the stimulus, from top row to the bottom, are as follows.

Back to Figure

The horizontal axis ranges from 8 to 0 then to 8 in increments of 0.5, with the midline along 0. The vertical axis ranges from negative 5 to 6 in increments of 0.5. The locations of the parts in the brain are tabulated below. All data are approximate.

A probe is in contact with the region A C E.

Back to Figure

The illustration shows a cannula consisting of an in tube surrounded by an out tube. The cannula is inserted into a cement cap, through the skull, and into the brain. Molecules in extracellular fluid diffuse through porous membrane at the base of the cannula. Fluid passes through the in tube and carries the diffused molecules through the out tube.

Back to Figure

1. A photo shows a patient lying on a narrow bed. The patient’s head is positioned inside a cylinder. In the foreground, a technologist observes images of brain on a computer screen.
2. An illustration shows an X-ray source and an X-ray detector positioned opposite to each other. The source and the detector rotate around the patient’s head.
3. A C T scan shows the ventral surface of the brain with a tumor on the right side of the brain.

Back to Figure

1. A magnetic resonance image shows a tumor in the parietal lobe of the brain.
2. A diffusion tensor image shows bundles of fibers in each hemisphere of the brain. The fiber bundle connecting the hemispheres is labeled T a, the bundle in the right anterior side is labeled R a f, the bundle in the right posterior side is labeled R s l f, the bundle in the left anterior side is labeled L a f, and the bundle in the left posterior side is labeled L s l f.

Back to Figure

The photo shows people protesting with megaphones and placards with the text, Stop Animal Research! Text reads, Thanks to animal research they’ll be able to protest 20.8 years longer. According to the U.S. Department of Health and Human Services, animal research has helped extend our life expectancy by 20.8 years. Of course, how you choose to spend those extra years is up to you. Foundation for Biomedical Research. To demonstrate your support, write the Foundation for

Biomedical Research, 818 Connecticut Avenue, N W Suite 303, Washington D C 20006. Or call (202) 457-0654.

PART II MOTIVATION AND EMOTION: WHAT MAKES US GO

Chapter 5. Drugs, Addiction, and Reward

Chapter 6. Motivation and the Regulation of Internal States

Chapter 7. The Biology of Sex and Gender

Chapter 8. Emotion and Health

5 DRUGS, ADDICTION, AND REWARD

© Neeta Lind

Psychoactive Drugs

Opiates and Opioids

A Further Look | A New Treatment for Pain: Botox

A Further Look | Government Agencies Act to Curb Overdose Deaths

Depressants

A Further Look | The Auto-Brewery Syndrome

Stimulants

Psychedelic Drugs

Marijuana

A Further Look | Changing Attitudes Toward Marijuana

Concept Check

Addiction

The Role of Reward in Addiction

Synaptic Plasticity and Addiction

Treating Drug Addiction

A Further Look | Targeting the Brain to Lessen Drug Withdrawal

Concept Check

The Role of Genes in Addiction

Separating Genetic and Environmental Influences

What Is Inherited?

Implications of Addiction Research

Concept Check

In Perspective

Chapter Summary

Study Resources

After reading this chapter, you will be able to

5.1 Identify the main classes of drugs.

5.2 Describe the effects of each class of drugs on the nervous system.

5.3 Predict how different drugs will affect behavior, based on the neural systems on which those drugs act.

5.4 Illustrate how the brain changes during addiction.

5.5 Discuss the role of learning in overdose and addiction.

5.6 Explain how pharmacology can be used to treat addiction.

5.7 Contrast the environmental and hereditary influences on addiction.

Honoré de Balzac (Figure 5.1) wrote a phenomenal 45 novels in 20 years. He was aided in his long writing marathons by large amounts of a stimulant drug whose effects pleased him so much that he advocated its use to others. However, he died at the age of 51, in part because of this unrelenting stimulation. What was the powerful drug that contributed both to his success and to his untimely death? According to his physician, Balzac died from a heart condition, aggravated by "the use or rather the abuse of coffee, to which he had recourse in order to counteract man's natural propensity to sleep" ("French Roast," 1996, p. 28).

Figure 5.1 Honoré de Balzac.

© The Print Collector/Alamy.

There is good reason to consider caffeine an addictive drug. Coffee may have milder effects than the other drugs coming out of Colombia, but strength of effect and illegality are not the criteria for classifying a substance as addictive. As you will see, a drug's effect on the brain is the telling feature, and that is our reason for discussing drugs at this particular point: It provides the opportunity to tie together our preceding discussions of brain structures and neural (particularly synaptic) functioning.

PSYCHOACTIVE DRUGS

A **drug** is a medicine or other substance that, on entering the body, changes the body's functioning. Drugs fall into one of two general classes, according to their effect on a transmitter system. As we saw in Chapter 2, an *agonist* mimics or enhances the effect of a neurotransmitter. It can accomplish this by having the same effect on the receptor as the neurotransmitter, by increasing the transmitter's effect on the receptor, or by blocking the reuptake or the degradation of the transmitter. An *antagonist* may occupy the receptors without activating them, simultaneously blocking the transmitter from binding to the receptors. Or it may decrease the availability of the neurotransmitter, for example, by reducing its production or its release from the presynaptic terminals.

Psychoactive drugs are those that have psychological effects, such as anxiety relief or hallucinations. The focus of this chapter is primarily on abused psychoactive drugs, although many of the principles discussed here are applicable more generally. We will discuss several psychotherapeutic drugs in the chapter on psychological disorders (Chapter 14). The effects of abused drugs are extremely varied, but whether they arouse or relax, expand the consciousness or dull the senses, addictive drugs produce a sense of pleasure in one form or another, at least initially. They also have several other effects in common; reviewing those effects will give us the language we need for a discussion of how the drugs work.

Most of the abused drugs produce **addiction**, which is identified by preoccupation with obtaining a drug, compulsive use of the drug in spite of adverse consequences,

and a high tendency to relapse after quitting. Many abused drugs also produce withdrawal reactions. **Withdrawal** is a negative reaction that occurs when drug use is stopped. Withdrawal symptoms are due at least in part to the nervous system's having adapted to the drug's effects, so they are typically the opposite of the effects the drug produces. For example, the relaxation, constipation, chills, and positive mood of heroin are replaced by agitation, diarrhea, fever, and depression during withdrawal. **Dependence** is the need to keep taking a drug to avoid the physical and psychological symptoms of withdrawal. A distinction is sometimes made between physical dependence, indicated by symptoms such as headaches, difficulty breathing, and racing heart, and psychological dependence, with symptoms such as anxiety, depression, sleep difficulties, and poor concentration and memory. But these distinctions are purely descriptive and not explanatory, because both types of dependence have a physiological basis. Addiction and dependence often occur together, but they are not synonymous and can occur separately; some drugs, such as antidepressants, result in dependence and withdrawal but are not addicting.

Regular use of most abused drugs results in **tolerance**, which means that the individual becomes less responsive to the drug and requires increasing amounts of the drug to produce the same results. Like withdrawal, tolerance results from compensatory adaptation in the nervous system; this involves reduction in receptor number or sensitivity, increased availability of enzyme to metabolize the drug, or increased reuptake by neurons or nearby glial cells. Tolerance is one reason for overdose, because tolerance can develop in response to the drug's pleasurable effects without developing in response to others. Thus, if the drug abuser takes larger doses of heroin to achieve the original sense of ecstasy while the tendency to produce sleep and respiratory arrest are undiminished, overdose is nearly inevitable, and the consequences can be deadly.

Opiates and Opioids

The **opiates** are drugs derived from the opium poppy (*Papaver somniferum*, see Figure 5.2). Opiates have a variety of effects: They are **analgesic** (removing pain), **hypnotic** (inducing sleep, which is where the flower gets its scientific name), and **euphoric** (creating a sense of happiness or ecstasy). Their downside is their addictive potential due to the euphoria. *Opium* has been used by humans since around 5700 BCE (Merlin, 2003). Originally it was eaten, but when explorers carried the Native Americans' practice of pipe smoking tobacco back to their native countries, opium users adopted this technique. *Morphine* was extracted from opium poppies at the beginning of the early 1800s and has been extremely valuable as a treatment for the pain of surgery, battle wounds, and cancer. Codeine, another ingredient of opium, has been used as a cough suppressant, and dilute solutions of opium, in the form of paregoric and laudanum (literally, "something to be praised"), were once used to treat diarrhea and to alleviate pain; paregoric was even used to quiet fretful children. Morphine continues to be used with cancer patients and is showing promise of safe use with milder pain in a time-release form that virtually eliminates the risk of addiction. Aside from morphine, opiates have mostly been replaced by synthetics. These are called *opioids*, to indicate that they are not derived from opium, at least not directly, though the term is increasingly used to include all substances that affect the endogenous receptors. Although the synthetic opioids are safer, they too are subject to abuse. You probably recognize one of them, OxyContin (oxycodone), because of its reputation for abuse rather than for its pain-relieving ability. Because of the problems associated with opiate abuse and misuse, scientists are on the lookout for safer substitutes; A Further Look introduces one promising treatment for chronic pain.

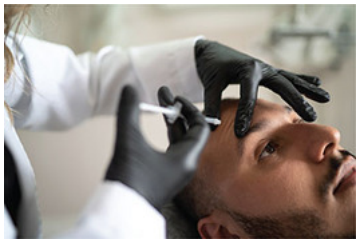
Figure 5.2 Opium Poppies.

© iStockphoto.com/Satirus

? Do opiates have any legitimate use?

A Further Look:

A New Treatment for Pain: Botox



FG Trade/Getty Images

You probably know that botulinum toxin (botox for short) is often used as a beauty treatment; when this bacterial toxin is injected into the forehead, it reduces wrinkles by temporarily paralyzing the muscles. Botox is proving very useful for other purposes as well, including the treatment of migraines, neck spasms, and even excessive sweating and leaky bladders. Dr. Maria Maiarù and her colleagues have created a novel compound (Derm-BOT) that joins type A botox (after it has been modified to eliminate its toxic effect) with an opiate called dermorphin; both botox A and dermorphin relieve pain, but the dermorphin gives the molecule affinity for opioid pain receptors (M. Maiarù et al., 2018). When the compound is injected, like in the photo, the dermorphin portion binds to opioid pain receptors; the botox portion then dissociates from the dermorphin and enters the neuron and prevents it from signaling pain. Dr. Maiarù's team was able to block pain for weeks in mice with spinal cord

injury. Pain relief was equivalent to the use of morphine, and because Derm-BOT's long-lasting effect would mean infrequent injections, there should be little risk of addiction. This novel strategy of adding opioid receptor affinity to a safer pain reliever might allow doctors to eliminate chronic pain without the side effects and addiction potential of standard opiates.

Heroin is the most notoriously abused opiate, due to its intense effect: a glowing, orgasm-like sensation that occurs within seconds, followed by drowsy relaxation and contentment. **Heroin** was synthesized from morphine in the late 1800s. In the early 1900s, it was marketed by the Bayer Drug Company of Germany as an over-the-counter analgesic, until its dangers were recognized. Three times more potent than morphine, heroin is now an illegal drug in the United States but is prescribed under strict conditions in Great Britain as a pain reliever and is used there and in a few European countries as a replacement drug in addiction treatment.

Because heroin is highly soluble in lipids, it passes the blood-brain barrier easily; the rapid effect increases its addictive potential. The major danger of heroin use comes from overdose—either from the attempt to maintain the pleasant effects in the face of increasing tolerance or because the user unknowingly obtains the drug in a purer form than usual. In a 33-year study of 581 male heroin addicts, 49% were dead at the end of the study, with an average age at death of 46 years (Hser, Hoffman, Grella, & Anglin, 2001). Nearly one fourth of those had died of drug overdoses (mostly from heroin); 19.5% died from homicide, suicide, or accident; and 15% died from chronic liver disease. Half of the survivors who could be interviewed were still using heroin, and the high likelihood of returning to usage even after 5 years or more of abstinence suggested to the researchers that heroin addiction may be a lifelong condition. Despite the representation of the horrors of heroin withdrawal in movies and on the Internet, it is best described as similar to a bad case of flu, so fear of withdrawal apparently is not the prime motivator for continued heroin addiction.

Opioid addiction has reached epidemic proportions in the United States; as a result, the number of overdose deaths involving opioids increased six-fold between 1999 and 2017. In 2017, 130 Americans died every day from opioid overdose, accounting for 68% of that year's 70,000 overdose deaths (Centers for Disease Control and Prevention, 2018). The severity of the crisis has led to several corrective measures described in A Further Look.

A Further Look:

Government Agencies Act to Curb Overdose Deaths

The U.S. attorney general has called the opioid epidemic "the worst drug crisis in American history" (Drug Enforcement Administration, 2018). Pharmaceutical companies have received part of the blame for allegedly encouraging physicians to prescribe opioids; the first of many lawsuits has been settled between Purdue Pharma, maker of OxyContin, and the state of Oklahoma for $270 million (Associated Press, 2019). Many critics also have faulted the U.S. Food and Drug Administration (FDA) for approving the drugs too readily, along with physicians' willingness to prescribe the drugs, which has closely paralleled the increase in deaths.

Under a plan instituted in 2016, the FDA will improve follow-up regarding safety and effectiveness of long-term opioid use, extend training of doctors, and encourage development of opioid drugs that are less likely to be abused. In addition, the Centers for Disease Control and Prevention released new guidelines that discourage primary care physicians from prescribing opioid medications for chronic pain (Dowell, Haegerich, & Chou, 2016). Moreover, the Drug Enforcement Administration is proposing a 10% cut in manufacturing quotas for the most frequently misused opioids (on top of a previous 20% cut), with the intent of reducing opioid prescriptions by one third within 3 years (Drug Enforcement Administration, 2018). Congress has stepped in as well, with legislation that targets programs to treat addiction and prevent substance abuse and overdoses and that provides financial incentives to encourage

substance abuse professionals to work in geographic areas hardest hit by drug overdoses (O'Reilly, 2018).

As tolerance to a drug develops, it also becomes associated with the person's drug-taking surroundings and circumstances. This learned or *conditioned tolerance* does not generalize completely to a new setting; when the person buys and takes the drug in a different neighborhood, the usual dose can lead to overdose (Macrae, Scoles, & Siegel, 1987; Siegel, 1984). Heroin is a particularly good example of this situational tolerance effect; an amount of heroin that killed 32% of rats injected in their customary drug-taking environment killed 64% of rats injected in a novel environment (Siegel, Hinson, Krank, & McCully, 1982).

We saw in Chapter 4 that neuroscientist Candace Pert discovered why opioid drugs are so effective as pain relievers: The body has receptors that are specific for these drugs, because it manufactures its own **endogenous** (generated within the body) opioids, known as **endorphins**. One effect of endorphins is pain relief, as you will see in Chapter 11. Stimulation of endorphin receptors triggers the pain-blocking effects of opiates; the euphoric effects occur from indirect activation of dopamine pathways.

Depressants

Depressants are drugs that reduce central nervous system activity. The group includes **sedative** (calming), **anxiolytic** (anxiety-reducing), and hypnotic substances. Alcohol, of course, is the most common and is the most abused in this class, so we will start there.

? What are the uses and dangers of depressant drugs?

Alcohol

Ethanol, or **alcohol**, is a drug fermented from fruits, grains, and other plant products containing sugar; it acts at many brain sites to produce euphoria, anxiety reduction, sedation, motor incoordination, and cognitive impairment (Koob & Bloom, 1988). Alcohol is the oldest of the abused drugs. There is evidence of beer making in the caves of Israel as far back as 9000 BCE (L. Liu et al., 2018), but alcohol consumption likely began far earlier when early humans discovered the pleasant effects of eating fallen fruit whose sugars had been fermented into alcohol by naturally occurring yeasts in the air. Drunkenness from this source has even been reported in animals, from elephants to butterflies (Dudley, 2002)! Alcohol has historically played a cultural role in celebrations and ceremonies, provided a means of achieving religious ecstasy, and, especially in primitive societies, permitted socially sanctioned temporary indulgence in hostility and sexual misbehavior. In modern societies, controlled group drinking has been replaced by uncontrolled individual abuse.

Alcohol is valued by moderate users as a social lubricant and as a disinhibitor of social constraints, owing largely to its anxiolytic effect. Like many drugs, its effects are complex. At low doses, say, a couple of drinks, it acts as a behavioral stimulant by increasing dopamine release and by turning off the inhibition the cortex normally exerts over behavior (Hendler, Ramchandani, Gilman, & Hommer, 2013). As intake increases, alcohol begins to have a sedative or even hypnotic effect; behavior moves from relaxation to sleep or unconsciousness. Imaging studies show that moderate or high doses of alcohol reduce activity throughout the brain and blunt the ability of the amygdala to distinguish threatening from neutral stimuli. The likely reason, as we will see shortly, is the combined reduction in glutamate activity and increased release of gamma aminobutyric acid. Later, after the bout of drinking has ended, the alcohol is metabolized back to a low blood level, and it becomes a stimulant again. That is why a few drinks in the evening may help you get to sleep at bedtime, only to awaken you later in the night.

Because alcohol interferes with cognitive and motor functioning as well as judgment, alcohol-impaired driving accounts for one third of all U.S. traffic fatalities (National

Highway Traffic Safety Administration, 2015). In the United States and Canada, a person is legally considered too impaired to drive when the blood alcohol concentration (BAC) reaches 0.08%. Alcohol is also closely linked with violent crime, accounting for an estimated 37% of violent victimizations (Greenfeld & Henneberg, 2001). Besides affecting judgment, alcohol reduces the anxiety that normally inhibits aggression (Pihl & Peterson, 1993). (Note that a rare few individuals can become intoxicated without imbibing at all, as A Further Look explains.)

A Further Look:

The Auto-Brewery Syndrome

The woman insisted she'd had very little to drink, but her BAC was 0.40%, so the police officer rushed her to the hospital (LaMotte, 2015). She should have been unconscious or worse, but she was only a bit woozy. In later testing with no alcohol, her BAC was double the legal limit at 9:15 a.m., triple the limit at 6:00 p.m., and more than four times the limit at 8:30 p.m. She was diagnosed with *auto-brewery syndrome*, also known as gut fermentation syndrome, which is a rare condition in which the intestines produce intoxicating levels of ethanol (Doucleff, 2013). With only 12 cases reported prior to 1972 (Iwata, 1972), there was skepticism about the legitimacy of the diagnosis (Logan & Jones, 2000). However, a recent review of cases has linked the symptoms to physiological conditions such as bowel dilation, short bowel syndrome, and an overabundance of intestinal yeast (B. T. Welch, Coelho Prabhu, Walkoff, & Trenkner, 2016). Treatments have included antibiotics, carbohydrate restriction, and antifungal therapy; the woman described in the example is being treated with antifungal medications and a yeast-free diet with no sugar, no alcohol, and low carbohydrates (Herbeck, 2015).

Alcohol carries with it a host of health and behavioral problems. High levels of any depressant drug have the potential to shut down the brain stem, resulting in coma or death; a BAC of 0.30% to 0.40% is life threatening, and BACs over 0.45% will usually be fatal (Lifeloc Technologies, n.d.). A common result of chronic alcoholism is cirrhosis of the liver, which in its severest form is fatal. In addition, the vitamin B1 deficiency that is associated with chronic alcoholism can produce brain damage and Korsakoff syndrome, which involves severe memory loss along with sensory and motor impairment (Figure 5.3). (We will talk more about this syndrome later in Chapter 12.) Binge drinkers are more likely to be impulsive and to have learning and memory impairments (Stephens & Duka, 2008). Alcohol is the fifth leading cause of premature death and disability globally and first among people between the ages of 15 and 49 (National Institute on Alcohol Abuse and Alcoholism, 2016). In the United States, the death toll is 88,000 each year (Stahre, Roeber, Kanny, Brewer, & Zhang, 2014). Even abstinence can be dangerous for people with alcoholism. Alcohol withdrawal involves tremors, anxiety, and mood and sleep disturbances; more severe reactions are known as **delirium tremens**—hallucinations, delusions, confusion, and, in extreme cases, seizures and possible death.

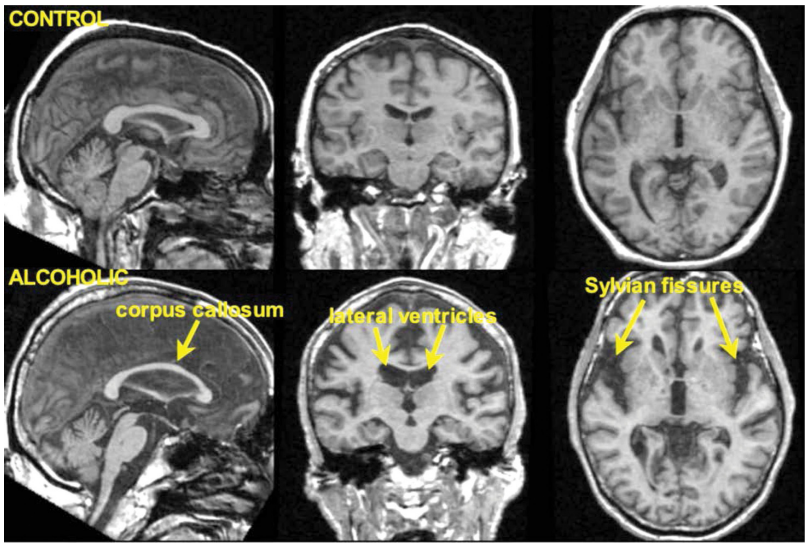


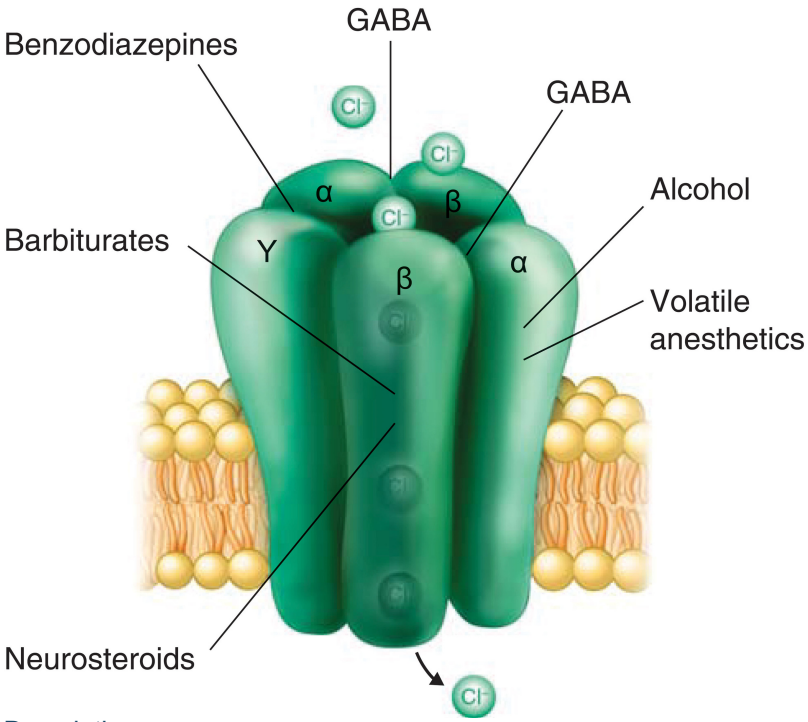
Figure 5.3 A Normal Brain and an Alcoholic Brain.
Both brains are from 53-year-old men. In the alcoholic brain, note the smaller corpus callosum, as well as the enlarged ventricles, sulci, and fissures, which indicate reduced brain tissue.

Source: From "Magnetic Resonance Imaging of the Living Brain," by Margaret J. Rosenbloom and Adolf Pfefferbaum, 2008, *Alcohol Research and Health*, *31,* pp. 362–376.

Considering the health risks, violence, and disruption of homes and livelihoods, alcohol is more costly to society than any of the illegal drugs. Excessive drinking costs the United States $249 billion per year—about $2.05 per drink—three quarters of it resulting from binge drinking (J. J. Sacks, Gonzales, Bouchery, Tomedi, & Brewer, 2015). In view of all the dangers of drinking, it seems amazing now that in 1961 a speaker at a symposium of psychiatrists and physicians on drinking expressed the group's consensus that "alcohol is the safest, most available tranquilizer we have" ("Paean to Nepenthe," 1961, p. 68).

Alcohol provides a good example of the complex effects that drugs have on multiple receptor and neurotransmitter systems. You may remember from Chapter 2, Table 2.2, that *glutamate* is the most prevalent excitatory neurotransmitter. Alcohol inhibits the release of glutamate, producing a sedating effect (Hoffman & Tabakoff, 1993; G. Tsai, Gastfriend, & Coyle, 1995). Later, there is a compensatory increase in the number of glutamate receptors, which probably accounts for the seizures that sometimes occur during withdrawal. Alcohol also increases the release of *gamma-aminobutyric acid (GABA)*, the most prevalent inhibitory neurotransmitter in the brain (Wan, Berton, Madamba, Francesconi, & Siggins, 1996). The combination of these effects results in sedation, anxiety reduction, muscle relaxation, and inhibition of cognitive and motor skills. Alcohol may also affect opiate receptors, resulting in the release of opioids and, in turn, increasing dopamine release (Advokat, Comaty, & Julien, 2018). Chronic alcohol consumption also increases serotonergic activity as well as the release of anandamide, which activates cannabinoid receptors. All these actions together likely account for the pleasurable aspects of drinking.

Alcohol specifically affects the A subtype of GABA receptor. Because the $GABA_A$ receptor is important in the action of other drugs, we give it special attention here. It is actually a receptor complex, composed of five different kinds of receptor sites (Figure 5.4). Two of the receptors respond to GABA. Their activation opens the receptor's chloride channel, and the influx of chloride ions hyperpolarizes the neuron. Other receptors in the complex respond to alcohol, to steroids, to barbiturates, and to benzodiazepines; these drugs enhance the binding of GABA to its receptor and thus its ability to open the chloride channel. Now you can understand why it is so dangerous to mix alcohol with barbiturates or benzodiazepines.



Description

Figure 5.4 The $GABA_A$ Receptor Complex.
The complex has binding sites for GABA, barbiturates, benzodiazepines, and alcohol, as well as other ligands.

Carolina Hrejsa/Body Scientific Intl.

? What prenatal effects does alcohol have?

Alcohol passes easily through the placenta, raising the BAC of a fetus to about the same level as the mother's. But, surprisingly, alcohol consumption was not considered detrimental to the developing embryo until 1973, when fetal alcohol syndrome (FAS) was identified (K. L. Jones & Smith, 1973; see Figure 5.5). FAS is characterized by intellectual impairment; additional symptoms may include hyperactivity, lack of focus, mood swings, hearing and vision deficiencies, poor coordination, low weight and height, and facial anomalies. The global rate of FAS is estimated at 0.15%; about 1 in 67 women who consumes alcohol during pregnancy delivers a child with FAS (Popova, Lange, Probst, Gmel, & Rhem, 2017). Regular alcohol abuse apparently is not required to produce damage. In one study, mothers who had children with FAS did not drink much more on average than the mothers of normal children, but they did report occasional binges of five or more drinks at a time (Streissguth, Barr, Bookstein, Sampson, & Olson, 1999). No safe level of alcohol intake during pregnancy has been established, so most authorities recommend total abstention. (Refer to Figure 3.26 to see the developmental effects of FAS on a mouse brain.)

Figure 5.5 Child With Fetal Alcohol Syndrome.
Besides intellectual impairment and behavioral problems, FAS individuals often have facial irregularities, including a short, upturned nose that is flattened between the eyes; a thin upper lip; and a lack of a groove between the nose and upper lip.

© George Steinmetz.

Barbiturates and Benzodiazepines

Like alcohol, **barbiturates** in small amounts act selectively on higher cortical centers, especially those involved in inhibiting behavior; in low doses, they produce talkativeness and increased social interaction, and in higher doses, they are sedatives and hypnotics. Barbiturates have been used to treat insomnia and prevent epileptic seizures, and from 1912 to 1960, they were the drug of choice for treating anxiety and insomnia (Advokat et al., 2018). They are not addictive in prescribed doses, but tolerance leads the person to increase the dosage, resulting in addictive symptoms similar to those of alcoholism. Like alcohol, barbiturates act at the $GABA_A$ complex, though at the barbiturate receptor; unlike alcohol, they can open chloride channels on their own in the absence of GABA. As a result, the line between therapeutic and toxic levels is a fine one, and their use has been fraught with accidental and intentional overdose (including famous cases such as Marilyn Monroe, Judy Garland, and Jimi Hendrix). As a result, barbiturates were mostly replaced by much safer benzodiazepines developed in the 1960s.

Benzodiazepines act at the benzodiazepine receptor on the $GABA_A$ complex to produce anxiety reduction, sedation, and muscle relaxation. They reduce anxiety by suppressing activity in the *limbic system*, a network of structures we will consider in more detail in the chapter on emotion (Chapter 8). In low doses, they moderate anxiety, agitation, and fear through their effects on receptors in the amygdala, orbitofrontal cortex, and insula, while GABA activation in the cortex and hippocampus results in confusion and amnesia (Advokat et al., 2018). Benzodiazepines are considerably safer than barbiturates because they cannot open chloride channels on their own.

There are numerous benzodiazepine drugs, the best known of which are Valium (diazepam), Ativan (lorazepam), Xanax (alprazolam), and Klonopin (clonazepam). One of the benzodiazepines, Rohypnol (roofies or rophies), has gained notoriety as the date rape drug. Because benzodiazepines are addictive and can produce mental confusion, safer alternatives have replaced them, and new drugs are actively being developed.

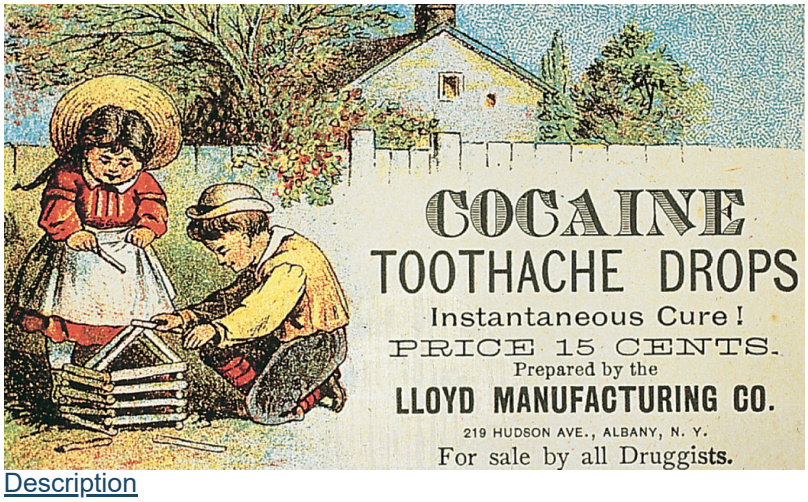
Stimulants

Stimulants activate the central nervous system to produce arousal, increased alertness, and elevated mood. They include a wide range of drugs, from the legal (caffeine) to the illegal (cocaine), which vary in the degree of risk they pose. The greatest danger lies in how they are used.

Cocaine

Cocaine, which is extracted from the South American coca plant, produces euphoria, decreases appetite, increases alertness, and relieves fatigue. The resulting coca paste is usually processed with hydrochloric acid into cocaine hydrochloride ("crystal" or "snow"), the familiar white powder that is administered intranasally ("snorted") or mixed with water and injected. Heat destroys this form, so it is not smokable. Pure cocaine, or *freebase*, is produced by removing the salt formed by the hydrochloric acid. Freebase can be smoked, and the vapor enters the bloodstream and reaches the brain in less than 10 seconds, making it very potent and addictive. The process involves volatile liquids and heat, so there is considerable danger of fire and explosions. A simpler chemical procedure was developed in the 1970s to yield *crack*, a solid form that is less pure but produces pure cocaine vapor when it is smoked. A crack user ingests 5 to 10 times as much cocaine as a person using the powder form of cocaine (Advokat et al., 2018). The low cost of crack has spread its use into poor urban communities where users could not afford cocaine.

Cocaine has not always been viewed as a dangerous drug. The coca leaf has been chewed by indigenous South Americans for centuries as a means of enduring hardship and impoverishment. When cocaine was isolated in 1855, it was initially injected as a local anesthetic. It soon found its way into over-the-counter medications (Figure 5.6), and from 1886 to 1906, Coca-Cola owed much of its refreshment to 60 milligrams of cocaine in every serving (M. S. Gold, 1997). Sigmund Freud, the father of psychoanalysis, championed the use of cocaine, giving it to his fiancée, sisters, friends, and colleagues and prescribing it to his patients. He even wrote an essay, which he called a "song of praise" to cocaine's virtues as an antidepressant, a fighter of chronic fatigue, and even a treatment for morphine addiction. He gave up the use of the drug, both personally and professionally, when he realized its dangers (Brecher, 1972). As a result of rising cocaine abuse and its links to criminal activity in the United States, Congress in 1914 enacted the Harrison Narcotics Act, which regulated its sale and use.

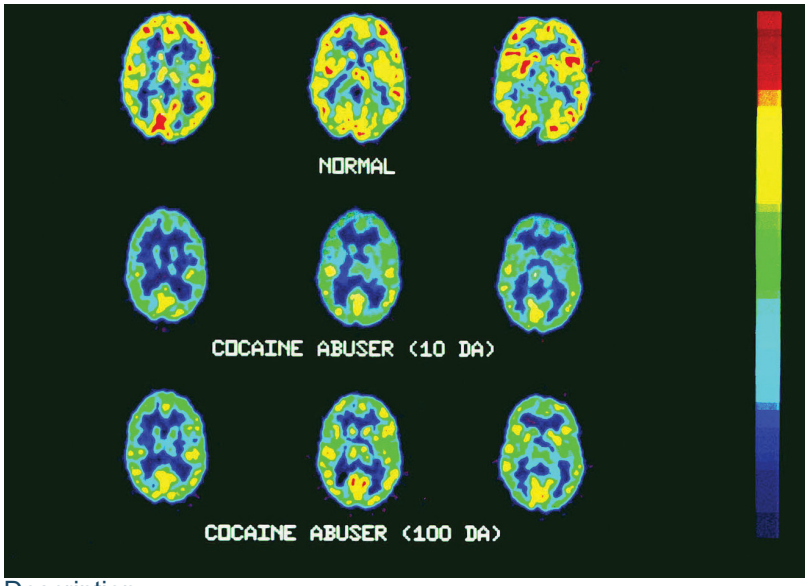


Description

Figure 5.6 Advertisement From Around 1900.

Source: The National Library of Medicine.

Cocaine blocks the reuptake of dopamine and serotonin at synapses, potentiating their effects. Dopamine usually has an inhibitory effect, so cocaine reduces activity in much of the brain, as the positron emission tomography (PET) scans in Figure 5.7 show (London et al., 1990). Presumably, cocaine produces euphoria and excitement because dopamine removes the inhibition the cortex usually exerts on lower structures. Reduced cortical activity is typical of drugs that produce euphoria, including benzodiazepines, barbiturates, amphetamines, alcohol, and morphine, although localized activation is often reported in frontal areas (R. Z. Goldstein & Volkow, 2002; London et al., 1990). Brain metabolism rises briefly during the first week of abstinence but then falls again during prolonged withdrawal; however, during craving, activity increases in several areas, as we will see later (R. Z. Goldstein & Volkow, 2002; S. Grant et al., 1996; Volkow et al., 1991; Volkow et al., 1999).



Description

Figure 5.7 A Normal Brain and a Brain on Cocaine.
The upper three scans show activity in a cocaine-free individual. The remaining scans show reduced activity in the brain of a cocaine abuser 10 days and 100 days after last cocaine use.

Science History Images / Alamy Stock Photo

Injection and smoking produce an immediate and intense euphoria, which increases the addictive potential of cocaine. After the end of a cocaine binge, the user crashes into a state of depression, anxiety, and cocaine craving that motivates a cycle of continued use. Withdrawal effects are typically mild, involving anxiety, lack of motivation, boredom, and lack of pleasure. Three decades ago, addiction was defined in terms of a drug's ability to produce withdrawal, and because cocaine's withdrawal symptoms are so mild, it was not believed to be addictive (Gawin, 1991). As usage increased in the population, we learned that cocaine is one of the most addictive of the abused drugs. The intensity of the drug's effect makes treatment for addiction very difficult, and no treatment is generally accepted as successful. Complicating rehabilitation is the fact that cocaine addicts typically abuse other drugs, and they have a very high rate of psychological disorders. These comorbidities include depression (67%), anxiety (30%), and paranoia (25%), as well as bipolar disorder, antisocial personality disorder, and attention-deficit/hyperactivity disorder (Advokat et al., 2018).

Cocaine users are likely to have impairments in memory and in executive functions, including impulse control, decision making, and assessment of emotional stimuli. These deficits are accompanied by reduced activity in the prefrontal cortex (Beveridge, Gill, Hanlon, & Porrino, 2008) and by a loss of gray matter in prefrontal

and temporal areas during middle age that is almost twice as fast as in nonusers (3.1 ml/year vs. 1.7 ml/year; Ersche, Jones, Williams, Robbins, & Bullmore, 2012).

Cocaine provides a good example of selective tolerance: While increasing amounts of the drug are required to produce the desired psychological effects, the person becomes supersensitive to the effect that produces seizures. It is possible that the risks of cocaine relative to other drugs have been underestimated. In one study, rats were allowed to press a lever that caused heroin or cocaine to be injected into their bloodstream; after 1 month, 90% of rats receiving cocaine had died of self-administered overdose, compared with 36% of rats receiving heroin (Bozarth & Wise, 1985).

Like alcohol, cocaine passes through the placenta easily, where it interferes with fetal development. It is difficult to separate the effects of abused drugs on a child's development from the effects of frequently co-occurring poverty and neglect, but a Toronto group was able to control environmental factors by studying 26 cocaine-exposed children who had been adopted. Compared with control children matched for the mother's IQ and socioeconomic status, the cocaine-exposed children had lower IQs, poorer language development, and greater distractibility (Nulman et al., 2001). In addition, we have evidence from animal studies that prenatal exposure to cocaine results in abnormal circuit formation among dopamine neurons (L. B. Jones et al., 2000).

? What neurotransmitter system is involved in the effects of all stimulant drugs?

Amphetamines

Amphetamines are a group of synthetic drugs that produce euphoria and increase confidence and concentration. The group includes amphetamine sulfate (marketed as Benzedrine), the three to four times more potent dextroamphetamine sulfate (marketed as Dexedrine), and the still more powerful methamphetamine (known on the street as *meth*, *speed*, *crank*, and *crystal*). Like cocaine, methamphetamine can be purified to its smokable, freebase form called *ice*. Because amphetamines dull the appetite, reduce fatigue, and increase alertness, they have been used by truck drivers, pilots, soldiers, and students to postpone sleep, and they appear in some prescription weight-loss drugs. They have also been used to treat ailments such as narcolepsy, a disorder of uncontrollable daytime sleepiness.

Amphetamines increase dopamine and norepinephrine release in the brain and interfere with reuptake of dopamine (Advokat et al., 2018). This combination of effects results in alert wakefulness, euphoria, excitement, reduced fatigue, and increased motor and speech activity. The effects of amphetamine injection are so similar to those of cocaine that individuals cannot tell the difference between the two (Cho, 1990).

Chronic methamphetamine use is associated with a five-fold increase in the risk of psychotic symptoms, and the risk doubles with concurrent frequent use of alcohol or cannabis (McKetin, Lubman, Baker, & Dawe, 2013). The symptoms mimic those of paranoid schizophrenia so closely that even trained professionals cannot recognize the difference, resulting in occasional emergency room mistreatment. In a laboratory study, a volunteer on amphetamine was convinced that a "giant oscillator" in the ceiling was controlling his thoughts. Another believed his ex-wife had hired an assassin to kill him and was perturbed when the doctor would not guard the window while he stood watch at the door (Griffith, Cavanaugh, Held, & Oates, 1972; S. H. Snyder, 1972). Long-term effects of chronic use include an 11% reduction in neural gray matter, an 11% loss of limbic tissue, and an 8% loss in the hippocampus, which is comparable to the deficit in Alzheimer's disease (Thompson et al., 2004).

Bath salts are a variety of synthetic drugs related to cathinone, a stimulant found in the khat (*Catha edulis*) plant; the name comes from labeling often used to disguise the illicit designer drugs. Chewing khat leaves for their stimulant effects is popular in Middle Eastern countries; in the movie *Captain Phillips*, it was the mainstay of the Somali pirates as they held the captain of the *Maersk Alabama* for ransom. Bath salts

increase levels of norepinephrine, dopamine, and serotonin; symptoms of severe intoxication include psychosis, delirium, dangerously combative or violent behavior, and physical effects that can lead to death (Baumann, 2014).

Nicotine

Nicotine is the primary psychoactive and addictive agent in tobacco. Tobacco is ingested by smoking, chewing, or inhaling (as snuff, a finely powdered form). Nicotine activates nicotinic acetylcholine (nACh) receptors, producing a stimulating effect, which by the end of a single cigarette becomes a relaxing, tranquilizing sensation as the nicotine desensitizes the receptors (Advokat et al., 2018). Nicotine produces reward effects by stimulating nACh receptors on dopamine neurons in the ventral tegmental area (VTA), causing them to release dopamine in the nucleus accumbens. It also increases dopamine release indirectly by releasing glutamate onto VTA dopamine neurons and by desensitizing nACh receptors on GABA neurons that normally inhibit dopamine release in the VTA.

The withdrawal reactions are well known because smokers "quit" so often. The most prominent symptoms are nervousness and anxiety, drowsiness, lightheadedness, and headaches. The United Kingdom annually observes a "No Smoking Day," similar to the "Great American Smokeout," in which people voluntarily abstain from smoking for a day; apparently, as a result of impairment from withdrawal symptoms, the number of workplace accidents increases by 7% on that day (Waters, Jarvis, & Sutton, 1998). Before bans on public and workplace smoking, about 80% of male smokers and two thirds of female smokers smoked at least one cigarette per waking hour (Brecher, 1972). In 2015, 68% of adult smokers wanted to quit, and 55% tried to quit during the year, but only 7% were successful (Babb, Malarcher, Schauer, Asman, & Jamal, 2017). Relapse is typical in smoking cessation attempts, but as of 2015, 60% of adults who had ever smoked had quit.

In part because usage is more continuous with tobacco than with other drugs, the health risks are particularly high, including for heart disease, stroke, and 17 types of cancer. The risks result not from nicotine but from about 250 harmful chemicals in the smoke. At least 60 of these produce cancer, many by damaging DNA throughout the smoker's body; smoking a pack of cigarettes per day for a year produces an estimated 130 mutations in each cell of the lungs and 97 mutations in the larynx (Alexandrov et al., 2016). Smoking may also cause brain damage; in smokers, gray matter volume is reduced in the prefrontal cortex, anterior cingulate cortex, insula, and olfactory gyrus, with the degree of loss corresponding to amount smoked (Fritz et al., 2014). In the United States, 40% to 50% of cigarettes are consumed by people with mental disorders (P. H. Smith, Homish, Giovino, & Kozlowski, 2014). Smoking is the leading preventable cause of death, accounting for 480,000 premature deaths annually in the United States and 6 million worldwide; the health and lost-productivity costs in the United States add up to $326 billion per year (Centers for Disease Control and Prevention, 2015b).

Cigarette package warnings aimed at expectant mothers are not just propaganda. Infants born to mothers who smoked during pregnancy have lower birth weight, a higher incidence of asthma, and up to 56% greater mortality (Gilliland, Li, & Peters, 2001; Kleinman, Pierre, Madans, Land, & Schramm, 1988; F. Rice et al., 2009). Recent studies have found evidence that maternal smoking impedes neuronal development in the fetus (Chatterton et al., 2017), and by the age of 6 to 8 years, the children have reduced cortical gray matter and overall brain volume, cortical thinning in prefrontal areas, and a tendency for depression (El Marroun et al., 2013). We saw in Chapter 4 that a link between maternal smoking and offspring outcome can be due to smoking in one case and to a hereditary association in another (F. Rice et al., 2009). A causal relationship for El Marroun's findings receives some credibility from the fact that children of women who quit smoking when they learned they were pregnant were no different from the children of nonsmoking mothers. A caveat, though, is that there may be important genetic differences between mothers who were able to give up smoking and those who weren't; these findings illustrate why we shouldn't be too quick to accept the "obvious" interpretation when two variables are correlated.

? How might nicotine affect developing brains?

As described in Chapter 2, nicotine stimulates nicotinic acetylcholine receptors. In the periphery, it activates muscles and may cause twitching. Centrally, it produces increased alertness and faster response to stimulation. Neurons that release dopamine contain nicotinic receptors, so they are also activated, resulting in a positive mood effect (Svensson, Grenhoff, & Aston-Jones, 1986).

Caffeine

Caffeine, the active ingredient in coffee and tea, produces arousal, increased alertness, and decreased sleepiness. Caffeine is the most widely consumed psychoactive drug in the world and is consumed daily by 85% of people in the United States (D. C. Mitchell, Knight, Hockenberry, Teplansky, & Hartman, 2014). Besides improving work performance, caffeine apparently has a number of health benefits if drunk in moderation (3 to 5 cups per day); several studies show a protective effect against cardiovascular disease, cancer, Parkinson's disease, Alzheimer's disease, depression, and driving accidents (Advokat et al., 2018). But as you saw in Balzac's case, it is subject to abuse. Consuming 12 or more cups of coffee per day can produce agitation, tremors, rapid breathing, and insomnia. Consuming about seven times that amount of caffeine—typically in the form of energy drinks or caffeine pills—can cause seizures and death, but just double the amount can be lethal if consumed over a short period of time (Sepkowitz, 2013).

Caffeine blocks receptors for the neuromodulator adenosine. Adenosine has sedative and depressive effects; blocking its receptors increases release of dopamine and acetylcholine and produces arousal (Silinsky, 1989; S. H. Snyder, 1997). Withdrawal symptoms include headaches, fatigue, anxiety, shakiness, and craving, which last about a week. Withdrawal is not a significant problem, because caffeinated beverages are in plentiful supply, but heavy drinkers may wake up with a headache just from abstaining overnight. In fact, researchers at the Mayo Clinic once recommended intravenous administration of caffeine to patients recovering from surgery to eliminate postoperative withdrawal headaches ("Caffeine Prevents Post-op Headaches," 1996).

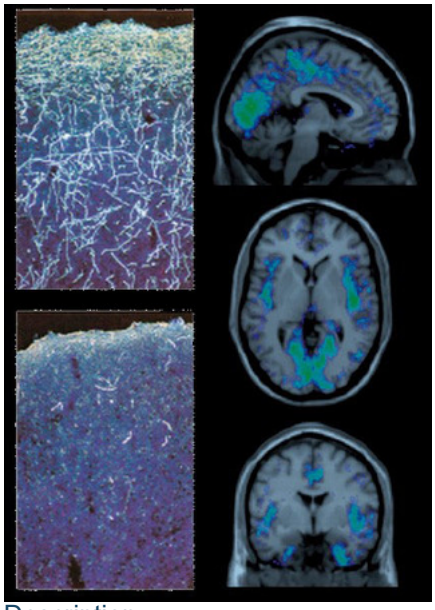
Psychedelic Drugs

Psychedelic drugs are compounds that cause perceptual distortions in the user. The term comes from the Greek words *psyche* ("mind") and *delos* ("visible"). "Visible mind" refers to the expansion of the senses and the sense of increased insight that users of these drugs report. Although the drugs are often referred to as *hallucinogenic*, they are most noted for producing perceptual distortions: Light, color, and details are intensified; objects may change shape; sounds may evoke visual experiences; and light may produce auditory sensations. Psychedelics may affect the perception of time, as well as self-perception; the body may seem to float or to change shape, size, or identity. These experiences are often accompanied by a sense of ecstasy, which makes recreational use of these substances common. Unlike other drugs of abuse, psychedelics are more often taken for their ability to alter subjective states of consciousness than for their rewarding effects. Though many of the psychedelic drugs are illegal, the Native American Church is allowed to use peyote in religious ceremonies (Advokat et al., 2018), and DMT (dimethyltryptamine) is permitted in several religions originating from Brazil (Pew Research Center, 2006). Psychedelics are classified in terms of their pharmacological effects; we will discuss three major groups, the serotonergic, the catecholaminergic, and glutaminergic NMDA receptor antagonists.

Serotonergic psychedelics are similar in structure and function to the neurotransmitter serotonin, and they stimulate serotonin receptors (Geyer & Vollenweider, 2008). (As you will see in this chapter and in later chapters, serotonin has a variety of psychological effects.) Psychological experiences include sensory distortions, such as warping of visual surfaces, repetitive geometric shapes, and intense colors, as

well as hallucinations. One of the best-known serotonergic psychedelics, *lysergic acid diethylamide (LSD)*, was popularized in the student peace movement of the 1960s and championed by the psychologist Timothy Leary. LSD is unusual among psychedelics, because it also stimulates dopamine receptors. Other psychedelics in this group include *psilocybin* and *psilocin* (LSD-like drugs from the mushroom *Psilocybe mexicana*) and *DMT* (a chemical extracted from a native flowering vine in the Brazilian Amazon). LSD, psilocybin, and DMT have been used experimentally in the treatment of psychological disorders, with varying degrees of success (Advokat et al., 2018).

Catecholaminergic psychedelics structurally resemble both amphetamine and catecholamine neurotransmitters (epinephrine, norepinephrine, and dopamine), which confers amphetamine-like properties along with the ability to produce psychedelic effects. The group includes mescaline (the active ingredient in peyote) and the synthetic drugs ecstasy and 2C-B. *Ecstasy* and *molly* are street names for *methylenedioxymethamphetamine* (we'll just call it MDMA); it became popular among young people through use at dance clubs and raves. Although health effects are usually minimal, MDMA increases heart rate and blood pressure and causes hyperactivity and hyperthermia. MDMA blocks norepinephrine and dopamine reuptake, but it also blocks reuptake of serotonin. At low doses, it is a *psychomotor stimulant* that increases energy, sociability, and sexual arousal; at higher doses, it produces hallucinatory effects like those of serotonergic psychedelics (Liechti & Vollenweider, 2000). The increase in serotonergic activity elevates mood, but the resulting depletion of serotonin levels produces a "crash" later. High doses or chronic use can be toxic to serotonergic neurons; studies have found significant neuronal loss in monkeys and, in humans, reductions in serotonergic activity throughout the cortex and in the hippocampus, as well as a 10.5% loss of hippocampal volume (Figure 5.8; den Hollander et al., 2012; S. J. Kish et al., 2010; McCann, Lowe, & Ricaurte, 1997; D. Wagner, Becker, Koester, Gouzoulis-Mayfrank, & Daumann, 2013). MDMA appears to have some redeeming value; combining the drug with psychotherapy may be useful for treating posttraumatic stress disorder (Mithoefer et al., 2018).



Description

Figure 5.8 Damage to Serotonergic Neurons Associated With Ecstasy Use.
Left: The top photo shows serotonin neurons (stained with a chemical that turns them white) in a normal monkey's brain; the bottom photo is from a monkey given MDMA a year earlier. Right: PET scans show reduced serotonergic activity (blue and green areas) in the brains of human MDMA users (blue and green areas).

Sources: From “Long-Lasting Effects of Recreational Drugs of Abuse on the Central Nervous System,” by U. D. McCann, K. A. Lowe, and G. A. Ricaurte, 1997, *The Neuroscientist, 3,* pp. 399–411. From “Decreased cerebral cortical serotonin transporter binding in ecstasy users: a positron emission tomography/[11C]DASB and structural brain imaging study,” by S. J. Kish, J. Lerch, Y. Furukawa, J. Tong, T. McCluskey, D. Wilkins, et al., 2010, *Brain, 133,* pp. 399–411.

NMDA receptor antagonists inhibit the N-methyl-d-aspartate type of glutamate receptor; these drugs are also known as *dissociatives*, because they cause more intense depersonalization and a sense of unreality. For example, ketamine (“special K”) produces a feeling of being disconnected from one’s body and the environment. Ketamine and phencyclidine (PCP, angel dust, or crystal) were developed as safer surgical anesthetics but were largely abandoned because they produced disorientation and hallucinations that were similar to the symptoms of schizophrenia (Mouri, Noda, Enomoto, & Nabeshima, 2007). These behavioral effects led to the current view that NMDA receptor dysfunction is involved in schizophrenia.

The rapid expansion of synthetic or “designer” drugs, which are created from chemicals rather than natural ingredients, is a special problem for drug enforcement. The ingredients themselves are often legal, the drugs are disguised as “bath salts” or “plant food” with the warning “not for human consumption,” and as lawmakers outlaw the specific drugs, underground chemists simply concoct new ones. Better known examples of synthetic psychedelics are LSD, MDMA, PCP, and 2C variants (including the most widely used 2C-B, commonly mislabeled as ecstasy at raves). The organic chemist Alexander Shulgin, who discovered the 2C family of phenethylamines, created many of these new drugs in the late 20th century. Through his research (mostly using himself and his friends as subjects), he described the psychological effects of more than 100 different drugs (Shulgin & Shulgin, 1991, 1997).

Marijuana

Marijuana is the dried and crushed leaves and flowers of the plant *Cannabis sativa* (Figure 5.9). The major psychoactive, *delta-9-tetrahydrocannabinol (THC)*, is usually consumed by smoking marijuana or mixing it in food. THC is particularly concentrated in the dried resin from the plant, which is called *hashish*.

Figure 5.9 Marijuana Plants.

© iStockphoto.com/Juanmonino

THC is a **cannabinoid**, a group of compounds that includes two known endogenous cannabinoids, anandamide and 2-arachidonyl glycerol (2-AG; Devane et al., 1992; di Tomaso, Beltramo, & Piomelli, 1996; Mechoulam et al., 1995). Cannabinoid receptors are found on axon terminals; cannabinoids are released by postsynaptic neurons and act as retrograde messengers, regulating the presynaptic neuron's release of neurotransmitter (R. I. Wilson & Nicoll, 2001). The receptors are distributed throughout the body; they are especially numerous in the frontal cortex, hippocampus, basal ganglia, and cerebellum, which accounts for the impaired cognitive functioning and distortions of time sense and perceptual processing, memory interference, and impairment of movement and motor coordination. THC increases dopamine release, which likely explains its pleasurable effects (mild euphoria, sense of well-being), but chronic use diminishes dopaminergic activity (Bloomfield, Ashok, Volkow, & Howes, 2016).

Marijuana may have a greater impact on users than previously thought. Long-term heavy users have various brain anomalies, including reduced volume in the hippocampus and amygdala and impaired white matter connectivity in the hippocampus and corpus callosum (Ashtari et al., 2011; Yücel et al., 2008; Zalesky et al., 2012). These findings are correlational, leaving open the possibility that the deficits were preexisting and contributed to excessive marijuana use; however, several animal studies have shown that cannabis does have neurotoxic effects on the hippocampus (cited in Yücel et al., 2008) and perturbs reward pathways in the brain (Friend et al., 2017). Longitudinal studies that had access to IQ measurements earlier in life also get around the correlational issue; one study showed that individuals who smoked five joints per day had an average 4-point decline in IQ from childhood to young adulthood (P. Fried, Watkinson, James, & Gray, 2002). In another study, individuals who used marijuana from their teens to age 38 lost an average of 6 IQ points (M.H. Meier et al., 2012). Abstinence apparently led to recovery of the losses in the first study but not in the second, probably due to longer use. In addition, the illegality of marijuana led to the development of synthetic marijuana, often with life-threatening results. In the summer of 2016, 33 individuals in Brooklyn were hospitalized after taking a form of synthetic marijuana called K2 (Rosenberg & Schweber, 2016).

There has been much less research on prenatal effects of marijuana, most likely because the impairments are not as obvious as those caused by prenatal exposure to cocaine and alcohol. Indeed, the studies that have been done found no deficits until about 4 years of age. Then, and through adolescence, data reveal behavioral problems, including impulsiveness and hyperactivity; decreased performance on visual-spatial tasks; and deficits in attention, memory, and language comprehension (P. A. Fried, 1995; C.-S. Wu, Jew, & Lu, 2011). These studies also suffer from being correlational, but experiments with animals have produced similar results.

Legalization is the major controversy surrounding marijuana; it is a battle that is being waged on two very different fronts. Because of the drug's mild effects, many people contend that its use should be unrestricted. Others, citing reports that it reduces pain, the nausea of chemotherapy, and the severity of the eye disease glaucoma, believe it should be available by a doctor's prescription. The medical claims have been controversial but are gaining acceptance, and both public and governmental attitudes are changing, as A Further Look indicates.

A Further Look:

Changing Attitudes Toward Marijuana

Although marijuana remains illegal under federal law, the U.S. Department of Justice has not been prosecuting medical use in states that have legalized it or recreational use as long as legalizing states maintain strict procedures for the sale of the drug. This reflects changing public attitudes toward marijuana as well as a desire to remove the criminal element and reduce demand for the more dangerous synthetic marijuana as well as other drugs. A 2018 Gallup poll indicated that 67% of Americans supported legalization of marijuana (McCarthy, 2018)—more than double the 31% approval 8 years earlier (Hartig & Geiger, 2018). Perhaps not surprisingly, young adults have had a large impact on this shift in public perception; 78% of adults 18 to 34 support marijuana legalization, but even those over 55 now surpass the majority level at 59%. So far, 33 states and Washington, DC, have legalized marijuana for medical purposes, and recreational use has been approved in 11 states and Washington, DC (Berke & Gould, 2019; J. O'Connor, 2019).

©iStockphoto.com/rasilja

? What are the two controversies about marijuana?

Another controversy concerns whether marijuana is addictive. The importance of this debate is that it requires us to define just what we mean by the term *addiction*. Addiction has traditionally been equated with a drug's ability to produce withdrawal symptoms; because marijuana's withdrawal symptoms are very mild, its compulsive use was attributed to "psychological dependence," a concept also invoked to explain the habitual use of other drugs that do not produce dramatic withdrawal symptoms, such as nicotine and caffeine. Withdrawal symptoms are mild because cannabinoids dissolve in body fats and leave the body slowly. However, monkeys will press a lever to inject THC into their bloodstream in amounts similar to doses in marijuana smoke inhaled by humans (Tanda, Munzar, & Goldberg, 2000). Researchers are reluctant to attribute drug self-administration in animals to psychological dependence and usually consider it evidence of addiction. Earlier we defined addiction in terms of the drug's hold on the individual, without reference to its ability to produce withdrawal symptoms. Next, we examine the reasons for taking this position.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- How does tolerance develop, and how does it increase a drug's danger?
- Why does alcohol increase the danger of barbiturates?
- How are the effects of amphetamine and cocaine at the synapse alike? How are they different?

ADDICTION

It is an oversimplification to assume that chronic drug use is motivated primarily by the pleasurable effects of the drug. In fact, individuals who engage in compulsive drug taking often report that they no longer enjoy their drug experience. Their casual drug use has progressed into the compulsive disorder of addiction. The common belief that addiction is fueled by the drug user's desire to avoid withdrawal symptoms

also has several flaws. First, it does not explain what motivates the person to use the drug until addiction develops. Second, we know that many addicts go through withdrawal fairly regularly to reset their tolerance level, so that they can get by with lower and less costly amounts of the drug. Third, it does not explain why many addicts return to a drug after a long period of abstinence and long after withdrawal symptoms have subsided. Finally, the addictiveness of a drug is unrelated to the severity of withdrawal symptoms (Leshner, 1997). Cocaine is a good example of severe addictiveness but mild withdrawal, while a number of drugs—including some asthma inhalers, nasal decongestants, and drugs for hypertension and angina pain—produce withdrawal symptoms but are not addictive (S. E. Hyman & Malenka, 2001).

? Why does the avoidance of withdrawal symptoms fail to explain addiction?

The Role of Reward in Addiction

Reward refers to the positive effect that an object or a condition—such as a drug, food, sexual contact, or warmth—has on the user. Reward is accompanied by a tendency to repeat the behavior that brought about the reward and, typically (in humans, at least), by feelings of pleasure. The most important reward circuit is the **mesolimbic pathway**, which consists of dopaminergic neurons originating in the **ventral tegmental area** and connecting to the **nucleus accumbens** and other targets (Figure 5.10). All addictive drugs target the mesolimbic dopamine system and increase dopaminergic activity in the nucleus accumbens. Dopaminergic inputs to the nucleus accumbens also are activated by natural reinforcers, such as food, water, and sexual activity (Malenka, Nestler, & Hyman, 2009).

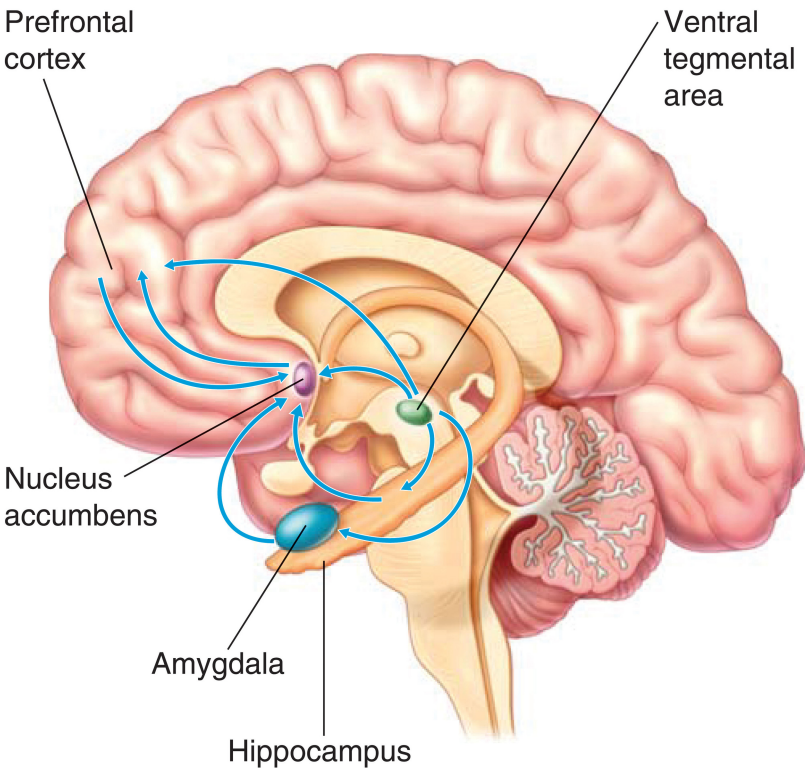


Figure 5.10 The Mesocorticolimbic Dopamine System.
The system is made up of the mesolimbic pathway and additional brain regions receiving dopaminergic projections from the ventral tegmental area, including the nucleus accumbens, prefrontal cortex, amygdala, and hippocampus. It is so named because it arises in the mesencephalic (midbrain) area and projects to the prefrontal cortex and the limbic system.

Christina Wheeler/Body Scientific Intl.

In 1954, James Olds accidentally mislocated an electrode in this general area and was surprised when his rat kept returning to the place where it had received electrical stimulation (Olds & Milner, 1954). We later learned that mild electrical stimulation to several brain locations activates the mesolimbic pathway (Fibiger, LePiane, Jakubovic, & Phillips, 1987). This so-called *brain stimulation reward* is thought to reflect "natural" reward processes, in part because effective sites are often in areas where experimenter-delivered stimulation evokes eating or sexual activity (Caggiula, 1970) and because humans as well as animals will press a lever to turn on the stimulation. It is more powerful than natural reinforcers, though, probably because it stimulates the reward circuitry directly rather than through peripheral nerves; as a result, animals will ignore food and water and tolerate painful foot shock in order to stimulate their brains with electricity, sometimes pressing a lever thousands of times in an hour. Drugs are similarly powerful: Humans will sacrifice their careers, relationships, and lives in the interest of acquiring and using drugs. While food and sex increase dopamine in the nucleus accumbens by 50% to 100%, drugs and electrical stimulation can have a three- to six-fold greater effect (A. G. Phillips et al., 1992; Wise, 2002).

? How is the reward system involved in addiction?

Although dopamine is the primary transmitter in the reward-addiction circuit, it is not the only one. While stimulants and nicotine act directly on dopaminergic neurons in the nucleus accumbens, others increase dopamine transmission indirectly—alcohol through GABAergic neurons and opiate-releasing neurons and opiates by stimulating opioid receptors and inhibiting GABAergic neurons. Regardless of a drug's initial effect, the final pathway involves the nucleus accumbens and increased dopamine transmission (Lüscher, 2016).

Synaptic Plasticity and Addiction

Reward motivates drug taking in the early stages, but addiction involves functional and structural changes in the brain that persist long after drug use ends and the drugs have cleared from the system (Lüscher, 2013). These changes occur in a broader area, the **mesocorticolimbic dopamine system**, which consists of the ventral tegmental area and the brain regions receiving its dopaminergic projections, including the nucleus accumbens, the prefrontal cortex, the amygdala, and the hippocampus (see Figure 5.10 again; Swanson, 1982). The nucleus accumbens serves an integrative role, combining judgments about goals and values from the prefrontal cortex with drug-related memories from the hippocampus and conditioned associations and emotional information from the amygdala to determine drug-seeking behavior (Floresco & Ghods-sharifi, 2007; S. E. Hyman, Malenka, & Nestler, 2006).

Initial exposure to addictive drugs—even a single dose—potentiates synapses between glutamate- and dopamine-releasing neurons in the VTA. With further drug use, potentiation in the VTA triggers more enduring neural changes in the form of increased dendrite length and greater synaptic complexity in the nucleus accumbens and prefrontal cortex (Robinson, Gorny, Mitton, & Kolb, 2001; Robinson & Kolb, 1997). Neural plasticity in response to drugs and drug-related stimuli increases, while plasticity with regard to other rewards diminishes (Gipson, Kupchik, & Kalivas, 2014). At the same time, baseline levels of dopamine activity decrease, resulting in tolerance and a decreased response to normal rewarding stimuli, while drugs and drug-related stimuli come to produce greater increases in dopamine transmission (Figure 5.11; Volkow, Fowler, Wang, & Swanson, 2004). This sensitization to the drug and drug-related stimuli is long-lasting, making the individual prone to relapse. Another effect is **hypofrontality**, reduced activity in several frontal regions that control working memory, attention, behavioral inhibition, and the individual's response to the environment. The impulsivity and compulsivity that characterize hypofrontality plus the decreased effectiveness of natural rewards refocus the individual's life on obtaining and taking the drug.

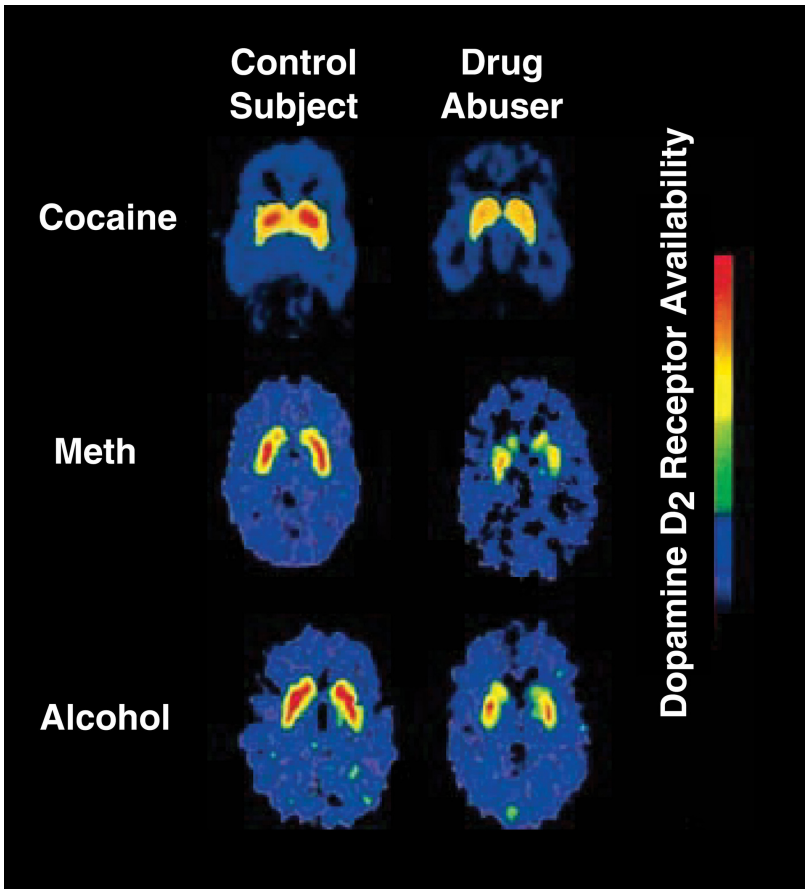


Figure 5.11 Reduced Dopamine D_2 Receptors in Drug Abusers.
The researchers imaged the brains using PET and an agent that binds to dopamine D_2 receptors. The predominance of yellow in place of red in the scans of the drug abusers' brains indicates fewer of the D_2 receptors than in the control subjects' brains.

Source: From "Role of Dopamine, the Frontal Cortex, and Memory Circuits in Drug Addiction: Insight From Imaging Studies," by N. D. Volkow et al., *Neurobiology of Learning and Memory,* 78, pp. 610–624. © 2002 Nora Volkow. Used with permission from Elsevier.

This structural plasticity and the involvement of dopamine and glutamate are similar to changes that occur during learning, leading many researchers to view addiction as a learning phenomenon. This is nowhere more evident than in craving, especially in its ability to persist years after years of abstinence. Presenting drug-related cues to cocaine-addicted rats initiates within 15 minutes a brief increase in synaptic potentiation in the nucleus accumbens (Gipson et al., 2014). Similarly, the sight of drug-related stimuli shifts the human addict's typically low brain metabolism to hyperactive in areas involved in learning and emotion (Figure 5.12; S. Grant et al., 1996; Volkow, Fowler, & Wang, 2004). The hippocampus is particularly important in learning associations with environmental stimuli; stimulating the hippocampus of rats that have given up pressing a lever because the drug delivery mechanism has been disconnected produces a 30-minute-long release of dopamine in the nucleus accumbens and a return to lever pressing (Vorel, Liu, Hayes, Spector, & Gardner, 2001).

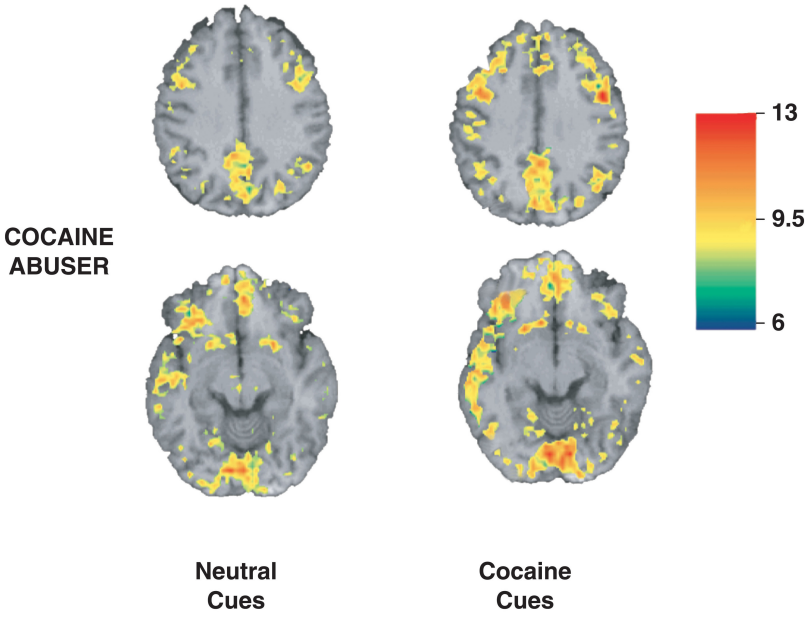


Figure 5.12 The Brain of a Cocaine Abuser During Craving.
PET scans are shown at two depths in the brain. Notice the increased activity during presentation of cocaine-related stimuli. Frontal areas and temporal areas are involved in learning and emotion.

Source: "Activation of Memory Circuits During Cue-Elicited Cocaine Craving," by S. Grant et al., 1996, *Proceedings of the National Academy of Sciences, USA*, 93, pp. 12040–12045. © 1996. National Academy of Sciences, U.S.A.

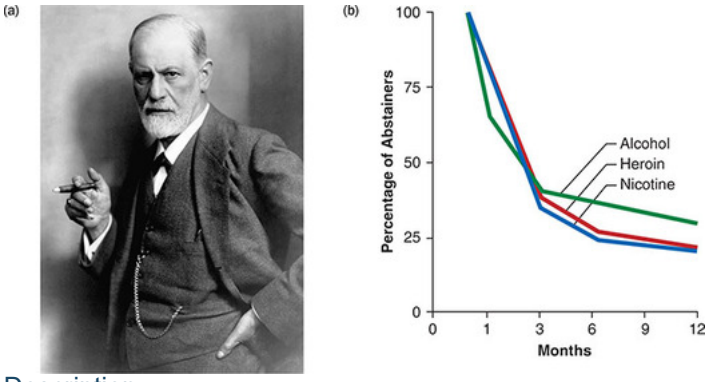
An intriguing feature of craving is that it increases progressively over the first weeks or months of drug abstinence, a phenomenon referred to as *incubation of craving* (Pickens, Theberge, Fanous, Hope, & Shaham, 2011). A good illustration of drug-induced plasticity is the potentiation of "silent" synapses that have developed over the course of addiction in glutamatergic pathways from the prefrontal cortex and the amygdala to the nucleus accumbens. The synapses are capable of releasing glutamate, but they lack the necessary receptors on the postsynaptic side; during withdrawal, the synapses mature and become functional. Unsilencing of these pathways produces craving, as evidenced by rats' increased drug seeking in the presence of drug-related cues (S.-Y. Lee et al., 2013; Ma et al., 2014).

We often hear that someone is "addicted" to eating or playing video games or some other non-drug-related behavior, but are these truly addictions? Several compulsive activities, such as gambling, eating, shopping, exercising, and sexual behavior, show addiction-like symptoms, including impaired control over the behavior, tolerance, withdrawal, craving, and high rates of relapse. The similarities are physiological as well. Human neuroimaging studies have shown that gambling, shopping, orgasm, playing video games, and the sight of appetizing food activate the mesocorticolimbic system (Olsen, 2011). In rats, there is evidence that sexual experience and long-term sugar consumption produce structural changes in the nucleus accumbens, including increased dendrites and dendritic spines and alterations in the balance of dopamine receptor types (Klenowski et al., 2016; Olsen, 2011). People being treated with dopamine agonists for Parkinson's disease experienced a 46% occurrence of these impulse-control disorders, suggesting that dopamine plays a role just as it does in drug abuse (Corvol et al., 2018). Although only gambling disorder is recognized by the psychiatric profession as a "behavioral addiction" (Robbins & Clark, 2015), these results suggest that drug abuse might be merely one example among a broad range of addictive disorders.

Treating Drug Addiction

Synanon, the residential community for the treatment of addictions, supplied its residents with all their food, clothing, and other necessities, including, until 1970, cigarettes—which alone cost $200,000 annually (Brecher, 1972). But then Synanon's founder and head Charles Dederich had a chest X-ray that showed a cloudy area in his lungs. He quit smoking and, realizing that residents as young as 15 were learning to smoke under his watch, stopped supplying cigarettes and banned their use on the premises. Giving up smoking was more difficult for the residents than expected. About 100 people left during the first 6 months, rather than do without cigarettes. Some of the residents who quit smoking noticed that they got over withdrawal symptoms from other drugs in less than a week, but the symptoms from smoking hung around for at least 6 months. As one resident said, it was easier to quit heroin than cigarettes.

Freud had a similarly difficult experience (Figure 5.13). He smoked as many as 20 cigars per day and commented that his passion for smoking interfered with his work. Although he quit cocaine with apparent ease, each time he gave up smoking, he relapsed. He developed cancer of the mouth and jaw, which required 33 surgeries, but he continued smoking. After replacement of his jaw with an artificial one, he was in constant pain and sometimes unable to speak, chew, or swallow, but still he smoked. He quit smoking when he died of cancer in 1939 (Brecher, 1972).



Description

Figure 5.13 Sigmund Freud and Relapse of Smoking Addiction.
Notice in the graph that the two legal drugs have relapse rates equal to that of heroin.

Source: (a) Bettmann/Getty Images. (b) Adapted with permission from "Nicotine Becomes Addictive," by R. Kanigel, 1988, *Science Illustrated*, Oct/Nov, pp. 12–14, 19–21. © 1988 *Science Illustrated*.

The first step in quitting drug use is detoxification. This means giving up the drug and allowing the body to cleanse itself of the drug residues. This is admittedly difficult with nicotine or opiates, but withdrawal from alcohol is potentially life threatening; medical intervention with benzodiazepines to suppress the withdrawal syndrome may be necessary (C. P. O'Brien, 1997). Still, withdrawal is often easier than the subsequent battle against relapse. The addict's impulsiveness, accompanied by atrophy and reduced activity in the orbitofrontal cortex, are even more pronounced in those who relapse (A. Beck et al., 2012; Dom, Sabbe, Hulstijn, & van den Brink, 2005), making therapy all the more difficult. However, in spite of the challenges, the relapse rate is no higher for drug addiction than for other chronic diseases such as hypertension, asthma, and type 2 diabetes (McLellan, Lewis, O'Brien, & Kleber, 2000). Fortunately, the number of treatment options is increasing, reflecting our improving knowledge of how addiction works.

Treatment Strategies

Agonist treatments replace an addicting drug with another drug that has a similar effect; this approach is the most common defense against drug craving and relapse. For example, nicotine gum and nicotine patches provide controlled amounts of the

drug without the dangers of smoking, and their use can be reduced systematically over time. Opiate addiction is often treated with a synthetic opioid called **methadone**. This treatment is controversial because it substitutes one addiction for another, but methadone is a milder and safer drug, and the person does not have to resort to crime to satisfy the habit. As a side note, methadone was developed in World War II Germany as a pain-relieving replacement for morphine, which was not available; it was called *adolphine*, after Adolph Hitler (Bellis, 1981). Addicts who do not benefit from methadone are sometimes given pharmaceutical-grade prescription heroin or the synthetic pain reliever hydromorphone as a means of deterring street use and criminal activity (Oviedo-Joekes et al., 2016).

Antagonist treatments, as the name implies, involve drugs that block the effects of the addicting drug. Drugs that block opiate receptors, such as naltrexone and naloxone, are used to treat opiate addictions and alcoholism because they reduce the pleasurable effects of the drug. Naloxone nasal spray is fast becoming a standard item in rescue kits as a powerful overdose-reversing drug and is saving lives. The potential for this type of treatment is illustrated dramatically in Figure 5.14 (Suzdak et al., 1986). However, antagonist treatment has a distinct disadvantage compared with agonist treatment. Because the treatment offers no replacement for the abused drug's benefit and it can cause rapid withdrawal symptoms, success depends on the addict's motivation to quit and willingness to comply with treatment. Medication implants help, because they last 3 to 6 months. Another strategy is to add an agonist, such as buprenorphine with naloxone, which reduces withdrawal symptoms.

Figure 5.14 Effects of a $GABA_A$ Receptor Blocker.
The two rats received the same amount of alcohol, but the one on the right received a drug that blocks the effect of alcohol at the $GABA_A$ receptor.

Source: National Institute of Mental Health. From G Kolata. "New drug counters alcohol intoxication." (1986). Science, 234(4781), 1198.

Rather than blocking the effects of a drug, **aversive treatments** cause a negative reaction when the person takes the drug. For example, Antabuse interferes with alcohol metabolism, so drinking alcohol makes the person ill. Similarly, adding silver nitrate to chewing gum or lozenges makes tobacco taste bad. As with antagonist treatments, success depends on the addict's motivation and treatment compliance.

All these approaches have problems: Alcoholics often fail to take Antabuse; methadone is itself addictive; naltrexone works with only a subset of addicts; and the anti-nicotine drugs Chantix and Zyban have been associated with hostility, depression, and suicidal thoughts. An attractive alternative is antidrug vaccines. **Antidrug vaccines** consist of molecules that attach to the drug and stimulate the immune system to make antibodies that will degrade the drug. These treatments avoid the side effects that occur when receptors in the brain are manipulated. Another benefit is that the antibodies are expected to last from weeks to years, which means that therapeutic success will not depend on the addict's decision every morning to take an anti-addiction drug. In rats, vaccines reduced the amount of cocaine reaching the brain by 80% (Carrera et al., 1995) and the amount of nicotine by 65% (Pentel et al., 2000); early human trials showed promise as well, but larger, more definitive trials have been disappointing (Martinez & Trifilieff, 2014). A significant problem with vaccines is that they do not reduce craving, and the number of antibodies produced is limited; the addict can increase drug intake and continue to get high.

Several abused drugs produce their own immune response in the brain when glia respond by initiating inflammation. Anti-inflammatory treatment is used to ease the symptoms of withdrawal, but because inflammation increases the excitability of dopaminergic neurons, it also may be effective against the addiction itself. Ibudilast, an inhibitor of glial activation, reduces self-administration of alcohol, methamphetamine, and opioids in rodents (Jacobsen, Hutchinson, & Mustafa, 2016). In Phase 2 human clinical trials, it reduced craving for tobacco, alcohol, cocaine, and heroin and decreased the rewarding effects of oxycodone while increasing its analgesic effects (MediciNova, 2018a), but it failed to increase abstinence from methamphetamine (MediciNova, 2018b). Another strategy, described in A Further Look, is an attempt to lessen withdrawal and keep addicts in treatment by applying electrical stimulation to the ear.

A Further Look:

Targeting the Brain to Lessen Drug Withdrawal

The current opioid epidemic in the United States is a major public safety problem that has law enforcement officials stymied. At the same time, it is a health concern that has sent doctors scrambling to find more effective treatments. One innovative approach involves reducing opioid withdrawal symptoms so that patients are more likely to remain in treatment. Adrian Miranda and Arturo Taca (2017) used the Bridge Neurostimulation System, a wearable acupuncture-like device originally developed to treat pain, to apply electrical stimulation to the ear. Their intent was to deliver stimulation over cranial nerves to brain areas involved in fear and pain to modify the patient's emotional perceptions during withdrawal. Over the 5 days that opioid-addicted patients used the device, withdrawal symptoms such as sweating, tremors, anxiety, and restlessness decreased significantly. Because treatment with the Bridge is nonpharmaceutical, it avoids the controversy about replacing one addicting substance with another (as occurs when using methadone as a treatment). And as a low-risk device, it readily won FDA approval as the first device for treating opioid withdrawal (U.S. Food and Drug Administration, 2017).

Addiction is difficult to treat, and the number of drugs approved for addiction therapy is quite limited (Table 5.1), forcing researchers to consider novel approaches. One intriguing new avenue involves chemical disruption of drug-related memories. Interfering with memory traces in the hippocampus by blocking acetylcholine receptors eliminated morphine relapse in mice (V. L. Wright et al., 2019), while transcranial magnetic stimulation reduced brain response to drug-related cues in human alcohol and cocaine users (Kearney-Ramos et al., 2018). The most novel approach took advantage of the fact that every time a memory is retrieved, it must be reconsolidated and is vulnerable during that time. Men who averaged drinking 30 pints of beer per week and wanted to cut down watched beer-related photos with a glass of beer in front of them. Minutes later, they were given a single high dose of ketamine, which blocks NMDA glutamate receptors that are important in memory formation. Although the control groups (who received a placebo injection with beer

photos or ketamine with orange juice photos) were motivated enough to reduce their drinking by 35%, the ketamine-with-beer group cut back their beer consumption by 50%. They were also the only ones who reported a significant reduction in their liking for beer and in their urge to drink a second beer (R. K. Das et al., 2019).

Table 5.1

TABLE 5.1 Medications Approved by the U.S. Food and Drug Administration for Treating Drug Addictions.

DRUG	MEDICATION	ACTION
Alcoholism	Disulfiram (Antabuse)	Inhibits aldehyde dehydrogenase. Aversive treatment.
	Naltrexone	Opioid receptor antagonist. Supposedly blocks reward; effectiveness questioned.
	Acamprosate	GABA agonist, glutamate antagonist. Reduces craving, unpleasant effects of abstinence.
Nicotine	Nicotine gum, patch, etc.	Replaces nicotine.
	Bupropion (Zyban)	Blocks reuptake of dopamine, norepinephrine, and serotonin.
	Varenicline (Chantix)	Enhances general reward but reduces nicotine reward; reduces withdrawal effects.
Heroin/ opiates	Naltrexone	Opioid receptor antagonist. Competes with opiates for receptor sites.
	Methadone	Replaces opiates at receptor.
	Buprenorphine, buprenorphine with naloxone (Suboxone)	Replaces opiates at receptor. Naloxone discourages abuse through injection.

Source: National Institute on Drug Abuse (2014).

Source: National Institute on Drug Abuse (2014).

Effectiveness and Acceptance of Pharmacological Treatment

Pharmacological intervention increases treatment effectiveness dramatically. Methadone combined with counseling produces abstinence rates of 60% to 80% in heroin addiction, compared with 10% to 30% for programs that rely on behavioral management alone (Landry, 1997). This is not an argument for pharmacological treatment alone. Drug addiction is almost always accompanied by environmental problems and emotional issues that must be dealt with, and therapeutic benefits are greater when medication is combined with psychosocial support (Strang et al., 2012).

A major difficulty in treating addiction is *comorbidity* with personality disorders, either mental or emotional. This means that drug abusers are likely to have other problems that complicate their rehabilitation. In a study of 43,000 people, 18% of drug abusers had an anxiety disorder, 20% had a mood disorder (most often depression), and 48% had a personality disorder (most often antisocial personality disorder; B. F. Grant, Stinson, Dawson, Chou, Dufour, & Compton, 2004; B. F. Grant, Stinson, Dawson, Chou, Ruan, & Pickering, 2004). These symptoms could be partly a by-product of the ravages of addiction, but drug abuse can also be the result of another disorder, for instance, when the person uses drugs as an escape or as a way to self-medicate the symptoms. However, it is more likely that the addiction and the personality disorder have a common genetic, neurological, or environmental cause.

Drug substitution treatment for addiction to heroin and other opioids has the strongest evidence of effectiveness (Strang et al., 2012), but giving a drug to combat another drug is controversial. Some people believe that recovery from addiction should involve the exercise of will and that recovery should not be easy. According to this perspective, Antabuse is okay because it causes the backslider to suffer, but methadone is not okay because it continues the pleasures of drug taking (Szalavitz, 2000). The counterargument is that the bottom line in drug treatment is effectiveness.

Addiction costs an estimated $600 billion each year in the United States alone (National Institute on Drug Abuse, 2012), and every dollar spent on addiction treatment returns more than $12 in increased healthcare savings and reduced criminality (National Institute on Drug Abuse, 2018). Even when the outcome of treatment is not abstinence, it can enable the addict to lead a healthy and productive lifestyle and avoid criminal activity.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- What is wrong with the withdrawal explanation of addiction?
- Describe the roles of reward and brain plasticity in addiction.
- What are the strengths and weaknesses of the different types of pharmacological treatment of addiction?

THE ROLE OF GENES IN ADDICTION

Much of the research on what predisposes a person to addiction has focused on alcoholism, to the neglect of other drugs. This is understandable, because alcoholism is such a pervasive problem in our society. Also, alcoholics are readily accessible to researchers because their drug use is legal. We are beginning to accumulate the same kind of information for other drugs, but as you will see, the study of alcoholism has served as a good model for other addiction research.

Separating Genetic and Environmental Influences

The heritability of addiction was first established with alcoholism. However, the role of heredity in alcoholism was controversial for a long time, because studies yielded inconsistent results. One reason for the inconsistency is that researchers typically treated alcoholism as a unitary disorder; they would study whatever group they had access to, such as hospitalized alcoholics, and generalize to all alcoholics. An important breakthrough came when Robert Cloninger and his colleagues studied all 862 men and 913 women who had been adopted by nonrelatives at an early age (an average of 4 months) in Stockholm, Sweden, between 1930 and 1949 (Bohman, 1978; Cloninger, 1987).

? How do hereditary and environmental contributions differ in the two types of alcoholism?

Cloninger identified two groups of alcoholics. Individuals with Type 1 alcoholism tended to be cautious and emotionally dependent; their problem drinking typically began after the age of 25 and was characterized by periods of abstinence followed by binge drinking fraught with guilt. Those with Type 2 alcoholism began drinking at a young age, drinking frequently and with little guilt. They showed signs of antisocial personality disorder: They were impulsive, uninhibited, confident, and socially and emotionally detached, and they frequently got into bar fights and were arrested for reckless driving. Most of them were male, and they made up most of the hospitalized population.

Later research showed that alcoholics do not always fit neatly into the two categories (Moss, Chen, & Hsiao-ye, 2007; Wennberg, Berglund, Berggren, Balldin, & Fahlke, 2014), but Cloninger produced groundbreaking revelations when he examined the offspring of the two groups. Those in the late-onset group were likely to become alcoholic only if they were reared in a home where there was alcohol abuse. But for the offspring of those with early-onset alcoholism, the rearing environment made no difference—evidence of a strong genetic influence that had eluded previous

researchers. Cloninger highlighted the complexity of heredity and environment in addiction. A more recent example comes from research with the *Met158* allele of the *COMT* gene, which is responsible for dopamine metabolism and is associated with an anxious, sensitive, and cautious personality. This cautiousness apparently confers some protection from alcoholism in American Plains Indians, but among European Caucasian men who tend to drink socially on a daily basis as a means of relaxing, *Met158* predisposes them to late-onset alcoholism (Enoch, 2006). A mutation of an opioid receptor gene (*OPRM1*) has also been linked to an increase in pleasurable effects from alcohol consumption in heavy drinkers (R. A. Ray et al., 2012).

What Is Inherited?

Obviously, not everyone who tries a drug becomes addicted; percentages run about 4% for inhalants, 9% for marijuana, 15% for alcohol, 17% for cocaine, 23% for heroin, and 32% for tobacco (Anthony, Warner, & Kessler, 1994). About 50% of addiction is due to heredity (Bevilacqua & Goldman, 2009); the rest is attributable to a host of environmental factors, including stress, social pressure, and drug exposure and availability (J. C. Wang, Kapoor, & Goate, 2012). Genetics research has implicated most of the major neurotransmitter systems (Dick & Agrawal, 2008), but for obvious reasons, genes that influence activity in the dopamine reward system have received the most attention. Kenneth Blum and his colleagues (2017) have developed a Genetic Addiction Risk Score based on 11 alleles of 10 genes; these alleles reduce activity in the dopamine system and produce a reward deficiency syndrome. The amino acid nutrient compound KB220 influences dopamine homeostasis mechanisms to increase reward functioning; administering KB220 has resulted in improvement in prefrontal networks, activation of the nucleus accumbens, and reduced drug craving and relapse.

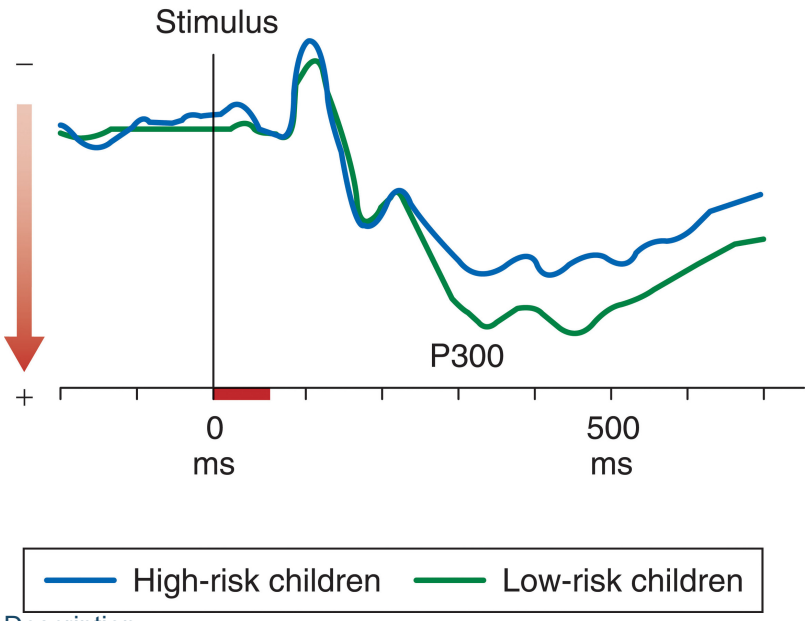
Genetic influences may increase an individual's vulnerability or provide protection; genes increase or decrease transmitter levels, regulate the number and sensitivity of receptors (for both neurotransmitters and the drug itself), and control metabolism of the drug. A study of 120,000 coffee drinkers is illustrative. The researchers identified eight gene locations that contribute to caffeine addiction (Coffee and Caffeine Genetics Consortium et al., 2015); their functions range from regulating the activity of dopamine, glutamate, and serotonin to the rapid metabolism of caffeine, so that the drinker is ready for another cup sooner. Four of the locations had previously been linked to smoking and obesity. Together, these gene locations explain only about 1.3% of the variation in caffeine intake. This suggests that many more genes are involved in caffeine addiction alone, and we can assume that the same is true for other forms of dependence.

Whether drug use will lead to addiction depends largely on how the individual reacts to the drug. For example, people with a particular allele of the *CHRNA5* acetylcholine receptor gene get a pleasurable rush during early experimentation with tobacco and are twice as likely to become addicted (C. D. Fowler & Kenny, 2014; Sherva et al., 2008). An allele of the opioid receptor gene *OPRMI* confers a similar euphoria from drinking and triples the risk of alcohol abuse (L. A. Ray & Hutchison, 2004); the risk is quadrupled in people resistant to the negative effects of alcohol (Schuckit, 1994). On the other hand, many Asians are protected from alcoholism because they experience intense flushing, nausea, and increased heart rate when drinking. This is due to excess oxidation of the alcohol to its toxic metabolite, acetaldehyde, or to reduced conversion of the acetaldehyde to acetate. Three alleles of the responsible genes (*ALH1B*2*, *ALDH1C*1*, and *ALDH*2*) are prevalent among Asians, and possession of one or more of them leads to a four- to nine-fold reduction in alcohol dependence (Eng, Luczak, & Wall, 2007). But, again, we see that genes influence behavior rather than determine it. As a heavy-drinking culture developed among Japanese businessmen, misuse of alcohol among those with the most protective of these alleles increased from 2.5% to 13% over a period of 13 years.

Impulsiveness, a major characteristic of the "addictive personality," is about 49% heritable (D. E. Gustavson, Miyake, Hewitt, & Friedman, 2014), and there is evidence linking impulsiveness to functional and structural brain anomalies in drug users. For example, the *GABRA2* gene influences $GABA_A$ receptor functioning; individuals with

two copies of a specific allele were higher in impulsiveness and had more symptoms of alcohol dependence (Villafuerte et al., 2012). When anticipating a reward or loss, these volunteers also showed more activity in the insular cortex, an area involved in food and drug craving, than did non-addicted individuals. People addicted to stimulant drugs have abnormal white fiber connectivity in prefrontal areas associated with impulse control, along with gray matter increases in temporal lobe areas involved in both addiction and learning (Ersche, Jones, Williams, Turton, Robbins, & Bullmore, 2012). The same characteristics are also found in non-addicted siblings of addicted individuals, which suggests that they are genetic in origin rather than a result of the alcohol abuse.

Alcoholics have a diminished P300 (P3) response, which is a dip in the EEG event-related potential that occurs about 300 milliseconds after an unexpected stimulus (Figure 5.15; Hesselbrock, Begleiter, Porjesz, O'Connor, & Bauer, 2001; S. Hill, 1995; W. G. Iacono, Carlson, Malone, & McGue, 2002). Reduced P3 has an estimated heritability of 64% (Hicks et al., 2007); in boys at age 17, it predicts the development of drug abuse disorders by the age of 20 (W. G. Iacono et al., 2002). Reduced P3 amplitude is seen in a variety of disorders characterized by behavioral disinhibition, the most distinctive characteristic of which is impulsivity. These include additional forms of drug abuse, as well as childhood conduct disorder and adult antisocial behavior.



Description

Figure 5.15 Evoked Potentials in Children at High Risk and Low Risk for Alcoholism. Evoked potentials were elicited by high-pitched tones occurring among low-pitched tones. The usual dip of the P300 wave is diminished in the high-risk children.

Source: Reprinted by permission of Elsevier Science from S. Y. Hill, D. Muka, S. Steinhauer, and J. Locke, "P300 Amplitude Decrements in Children From Families of Alcoholic Female Probands," *Biological Psychiatry, 38*, pp. 622–632. © 1995 Society of Biological Psychiatry. Used with permission from Elsevier.

This discussion would be incomplete if we left the impression that the link between genes and drug use is unidirectional; drugs also change the way our genes function. A recent study of smokers and former smokers found more than 7,000 genes whose functioning had been modified by the process of methylation (Joehanes et al., 2016); **methylation** is the attachment of a methyl group to DNA, which suppresses a gene's activity. The changes were found most reliably on genes associated with smoking-related diseases, including cardiovascular disease and certain types of cancer. Although most of these changes had disappeared after 5 years of nonsmoking, some

persisted as long as 30 years, which may explain why smoking-related diseases can occur decades after a person stops smoking. Even more disturbing is that a mother's smoking has similar effects on the genes of her unborn fetus (Joubert et al., 2016). The genes affected in the offspring are related to lung and nervous system development; smoking-related cancers; and birth defects associated with prenatal smoking, such as cleft lip and cleft palate. Surprisingly, evidence is mounting that paternal smoking prior to pregnancy causes gene mutations in the offspring, increases the risk of birth defects and childhood cancers (Beal, Yauk, & Marchetti, 2017), and reduces fertility by half in male offspring (Axelsson et al., 2018).

Implications of Addiction Research

The study of drug abuse and addiction has practical societal importance, but it is worthwhile for other reasons as well, particularly in shedding light on other kinds of vulnerability and principles of behavioral inheritance. For example, the fact that genetic and environmental influences operate differently in different types of alcoholism and in different cultural settings demonstrates that no behavior is simple or simply explained. Even after we understand the relative roles of heredity and environment, there is further complexity, because we must also understand the mechanisms—the neurotransmitters, receptors, pathways, enzymes, and so on. In other words, the causes of addiction, and of behavior in general, are many and complex. Finally, we must look beyond simple appeals to willpower in explaining the self-defeating behavior of the addict, just as we must do when we try to understand other kinds of behavior. Our brief look at addiction is a good preparation for our inquiries into the physiological systems behind other human behaviors and misbehaviors.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- How did the failure to recognize two types of alcoholism create misunderstandings about hereditary and environmental influences and gender distribution in alcoholism?
- How can lowered sensitivity to a drug increase the chances of addiction?
- What are two kinds of evidence that some people are predisposed to alcoholism from birth?

IN PERSPECTIVE

The costs of drug abuse include untold suffering; loss of health, productivity, and life; and billions of dollars in expenses for treatment and incarceration. The only upsides are that the study of drug abuse reveals the workings of the synapses and brain networks and helps us recognize that powerful biological forces are molding our behavior. This knowledge in turn helps us understand the behaviors that are the subject of the remaining chapters, including the disorders covered there, and guides research into developing therapeutic drugs.

Chapter Summary

Psychoactive Drugs

- Most abused drugs produce addiction, which is usually (but not always) accompanied by withdrawal symptoms when drug use is stopped.
- Tolerance can increase the dangers of drugs, because tolerance to life-threatening effects may not develop.
- The opiates have their own receptors, which are normally stimulated by endorphins.
- The opiates are particularly addictive and dangerous.
- Depressants reduce activity in the nervous system. Some of them have important uses, but they are also highly abused.
- Stimulants increase activity in the nervous system. They encompass the widest range of effects and include nicotine, most notable for its addictiveness and its association with deadly tobacco.
- Psychedelic drugs are interesting for their perceptual/hallucinatory effects, which result from their transmitter-like structures.
- Marijuana is controversial not just in terms of the issue of legalization but also because it raises questions about what constitutes addiction.

Addiction

- The mesolimbic pathway is a reward circuit that plays a role in drug addiction, feeding, sex, and other behaviors. Synaptic plasticity in the mesocorticolimbic dopamine system maintains drug seeking.
- Dopamine contributes to addiction through its role in learning by modifying neural functioning.
- Treatment of addiction is very difficult; effective programs combine psychological support with pharmacological strategies, including agonist, antagonist, and aversive treatments and, potentially, drug vaccines.

The Role of Genes in Addiction

- Research suggests that addiction is partially hereditary; some effects are general and others are drug-specific.
- Research indicating that there are at least two kinds of alcoholism suggests that the relationship between heredity and environment in addiction is complex.
- Genes may increase vulnerability to addiction or provide protection, by regulating transmitter levels, number and sensitivity of receptors, and metabolism of the drug.

- Addicts have transmitter and receptor irregularities and structural and functional brain anomalies that appear to be genetic in origin.

Study Resources

For Further Thought

- Is the legality or illegality of a drug a good indication of its potential for abuse?
- Is it morally right to treat addictions with drug antagonists, aversive drugs, and antidrug vaccines? Is your opinion the same for drug agonists?
- You work for an agency that has the goal of substantially reducing the rate of drug abuse in your state through education, family support, and individualized treatment. Based on your knowledge of addiction, what elements should the program include?

Test Your Understanding

1. Describe the separate roles of reward and brain plasticity in addiction.
2. What are the practical and ethical considerations in using drugs to treat addiction?
3. Sally and Sam have alcoholism. Sally seldom drinks but binges when she does and feels guilty later. Sam drinks regularly and feels no remorse. What other characteristics would you expect to see in each, and what speculations can you make about their environments?
4. Discuss how genes contribute to addiction, giving examples.

Select the best answer:

1. In the study of conditioned tolerance to heroin,
    1. human subjects failed to show the usual withdrawal symptoms.
    2. human subjects increased their drug intake.
    3. rats were unresponsive to the drug.
    4. rats tolerated the drug less in a novel environment.
2. Withdrawal from alcohol
    1. can be life threatening.
    2. is about like a bad case of flu.
    3. is slightly milder than with most drugs.
    4. is usually barely noticeable.
3. Alcohol, barbiturates, and benzodiazepines are deadly when taken together because they
    1. affect the thalamus to produce almost total brain shutdown.
    2. have a cumulative effect on the periaqueductal gray.
    3. affect the same receptor complex.
    4. increase dopamine release to dangerous levels.
4. Psychedelic drugs often produce hallucinations by
    1. inhibiting serotonin neurons.
    2. stimulating serotonin receptors.
    3. stimulating dopamine receptors.
    4. blocking dopamine reuptake.
5. Marijuana was the subject of disagreement among researchers because some of them
    1. believed it is more dangerous than alcohol or tobacco.
    2. believed it is highly addictive.
    3. thought it failed to meet the standard test for addictiveness.
    4. overstated its withdrawal effects.
6. Evidence in the text that addiction does not depend on the drug’s ability to produce withdrawal symptoms is that

    1. they never occur together with the same drug.
    2. they are produced in different parts of the brain.
    3. either can be produced without the other in the lab.
    4. addiction occurs in the cortex, but withdrawal occurs in the peripheral nervous system.
    5. the same addictive drug can cause withdrawal in some people but not others.
7. In the reward pathway, dopamine
    1. is the only transmitter involved.
    2. is the primary transmitter.
    3. is one of two transmitters.
    4. is involved with some drugs but not others.
8. The best argument that caffeine is an addictive drug like alcohol and nicotine is that
    1. it is used regularly by most of the population.
    2. users progressively increase their intake.
    3. it affects the same processes in the brain.
    4. it stimulates dopamine receptors directly.
9. The mesocorticolimbic system includes the
    1. ventral tegmental area and nucleus accumbens.
    2. ventral tegmental area, nucleus accumbens, and prefrontal cortex.
    3. ventral tegmental area, nucleus accumbens, prefrontal cortex, and amygdala.
    4. ventral tegmental area, nucleus accumbens, prefrontal cortex, amygdala, and hippocampus.
10. If you work in a medical clinic in an area with frequent heroin overdoses, which type of drug would be most helpful to have on hand?
    1. Agonists such as methadone
    2. Antagonists such as naloxone
    3. Aversives such as Antabuse
    4. Anxiolytics such as clonazepam
11. Critics of treating drug addiction with drugs believe that
    1. getting over addiction should not be easy.
    2. drugs such as Antabuse are dangerous themselves.
    3. the drugs are not very effective and delay effective treatment.
    4. a and b
    5. b and c
12. The type of alcoholism in which the individual drinks regularly is associated with
    1. behavioral rigidity.
    2. perfectionism.
    3. feelings of guilt.
    4. antisocial personality disorder.
13. Alcoholics often
    1. have reduced serotonin and dopamine functioning.
    2. are more sensitive to the effects of alcohol.
    3. are unusually lethargic and use alcohol as a stimulant.
    4. have an inherited preference for the taste of alcohol.

Answers:

1. d, 2. a, 3. c, 4. b, 5. c, 6. b, 7. b, 8. c, 9. d, 10. b, 11. a, 12. d, 13. a.

For Further Reading

1. Often used as a text in psychopharmacology and upper-level behavioral neuroscience courses, *Julien's Primer of Drug Action*, by Claire Advokat, Joseph Comaty, and Robert Julien (14th ed., Worth, 2018), covers principles of drug action, properties of specific drugs, pharmacotherapy for various disorders, and societal issues. It is a #1 best seller in Medicine and Psychology at Amazon, where it receives good reviews from students.
2. *Buzzed: The Straight Facts About the Most Used and Abused Drugs From Alcohol to Ecstasy*, by Cynthia Kuhn, Scott Swartzwelder, and Wilkie Wilson (5th ed., Norton, 2019), gives technical information about drugs written in a style

appropriate for college students. This handbook covers drug characteristics, histories of the drugs, addiction, the workings of the brain, and legal issues.
3. *Dreamland: The True Tale of America's Opiate Epidemic*, by Sam Quinones (Bloomsbury, 2016), has received numerous awards, including the National Book Critics Award, for its account of the origins of the country's opiate crisis. There is also a young adult version of this book.
4. "Medical Cannabis: What You Really Need to Know," by Graham Lawton (*New Scientist*, August 4, 2018, pp. 29–33), discusses the 80 conditions for which cannabis has been claimed effective, along with questions about what it does and how.

Key Terms

addiction 130

agonist treatment 148

alcohol 133

amphetamine 138

analgesic 131

antagonist treatment 149

antidrug vaccine 149

anxiolytic 133

aversive treatment 149

barbiturate 136

bath salts 139

benzodiazepine 136

caffeine 140

cannabinoids 142

cocaine 137

delirium tremens 135

dependence 130

depressant 133

drug 130

endogenous 132

endorphins 132

euphoric 131

heroin 131

hypnotic 131

hypofrontality 146

marijuana 142

mesocorticolimbic dopamine system 146

mesolimbic pathway 145

methadone 148

methylation 154

nicotine 139

nucleus accumbens 145

opiate 131

psychedelic drug 141

psychoactive drug 130

reward 145

sedative 133

stimulant 137

tolerance 130

ventral tegmental area 145

withdrawal 130

Descriptions of Images and Figures

Back to Figure

The complex consists of five receptor sites: two alpha, two beta, and one gamma. The compounds inducing response from each site are as follows:

- Alcohol and volatile anesthetics activate alpha sites.
- Barbiturates and neurosteroids activate beta sites.
- G A B A activates alpha and beta sites.
- Benzodiazepines activate gamma site.

Negative chloride ions from extracellular fluid pass through the receptor complex and enter the cell.

Back to Figure

The poster features two children playing with sticks behind a fence. Text reads, Cocaine toothache drops. Instantaneous cure! Price 15 cents. Prepared by the Lloyd Manufacturing Company. 219 Hudson Avenue, Albany, N Y. For sale by all druggists.

Back to Figure

Each set consists of three scans. The scans for normal brain show high level of activity. The scans for brain of a cocaine abuser 10 days after last cocaine use show low level of activity. The scans for brain of a cocaine abuser 100 days after last cocaine use show moderate level of activity.

Back to Figure

There are two images in the first set. The first image shows a network of serotonergic neurons in the brain of a monkey. The second image shows absence of the serotonergic network.

The second set shows three human brain scans with sagittal, transverse, and coronal views. The scans show reduced serotonergic activity, depicted by blue and green areas in different parts of the brain.

Back to Figure

The horizontal axis of the graph is labeled months, ranging from 0 to 12, and the vertical axis is labeled percentage of abstainers, ranging from 0 to 100 in increments of 25. The approximate data from the graph are tabulated below.

Back to Figure

The horizontal axis ranges from negative 200 to 700 milliseconds in increments of 100. An arrow pointing downward toward the axis is labeled with a negative sign at its tail and a positive sign at its head. The stimulus is given at 0 milliseconds. The curves for high-risk and low-risk children is initially constant, peaks, decreases to a minimum, and then increases. The minimum for low-risk children is lesser than the minimum for high-risk children. The curve for low-risk children is labeled P 300.

6 MOTIVATION AND THE REGULATION OF INTERNAL STATES

© iStockphoto.com/CathyKeifer

Motivation and Homeostasis

- Theoretical Approaches to Motivation
- Simple Homeostatic Drives

Concept Check

Hunger: A Complex Drive

- Gustation: The Role of Taste

A Further Look | Predator Control Through Learned Taste Aversion

- Digestion and the Two Phases of Metabolism
- The Hypothalamic Circuitry of Hunger
- Signals That Initiate and Terminate Eating
- Long-Term Controls

A Further Look | How Nicotine and Marijuana Affect Appetite

Concept Check

Obesity

A Further Look | Diabetes, the Duck-Billed Platypus, and the Cone Snail

The Myths of Obesity

The Contributions of Heredity and Environment

A Further Look | Obesity Alters Your DNA

Obesity and Reduced Metabolism

Treating Obesity

A Further Look | Pets May Provide Protection Against Obesity

Concept Check

Anorexia, Bulimia, and Binge Eating Disorder

Environmental and Genetic Contributions

The Role of Neurotransmitters

Concept Check

In Perspective

Chapter Summary

Study Resources

After reading this chapter, you will be able to

6.1 Summarize the psychological theories of motivation.

6.2 Describe how temperature regulation and thirst reflect the concept of homeostasis.

6.3 Explain the role of taste in choices of food.

6.4 Identify the brain signals that control when we begin and end eating.

6.5 Understand the truths and myths of obesity.

6.6 Compare the roles of environment and heredity in risk for obesity.

6.7 Examine how the environment and genetics impact risk for disordered eating.

6.8 Discuss the role of neurotransmitters in eating disorders.

When Christopher was born, it was obvious there was something wrong (Lyons, 2001). He was a “floppy baby,” lying with his arms and legs splayed lifelessly on the bed, and he didn’t cry. Doctors thought he might never walk or talk, but he seemed to progress right until grade school, when he was diagnosed with Prader-Willi syndrome. Christopher had most of the symptoms: He stopped growing at 5 feet, 3 inches (1.6 meters), he had learning difficulties, and he had difficulty with impulse control. The disorder occurs when a small section of the father’s chromosome 15 fails to transfer during fertilization or the genes there are turned off. Although we don’t know which genes in that part of the chromosome cause the disorder, we do know that individuals with Prader-Willi have an excess of a hormone that increases appetite (Cummings et al., 2002) and a deficit in neurons that inhibit eating (J. L. Miller et al., 2017).

More obviously, Christopher could never seem to recognize when he had eaten enough, so he ate constantly. He even stole his brother’s paper-route money to buy snacks at the corner store. At school, he would retrieve food from the cafeteria garbage can and wolf it down; his classmates would taunt him by throwing a piece of food in the trash to watch him dive for it. The only way to protect a person like Christopher is to manage his life completely, from locking the kitchen to institutionalization. State law did not permit institutionalization for Christopher, because his average-level IQ did not fit the criterion for inability to manage his affairs. He lived in a series of group homes but was thrown out of each one for rebelliousness and violence, behaviors that are characteristic of the disorder. When he died at the age of 28, he weighed 500 pounds (227 kilograms; Figure 6.1).

Figure 6.1 Christopher During a Hospital Stay.

Source: Courtesy of the San Luis Obispo County Tribune

In Chapter 5, we puzzled over why people continue to take drugs that are obviously harming them. Now we are forced to wonder why a person would be so out of control

that he would literally eat himself to death. When we ask why people (and animals) do what they do, we are asking about their motivation.

MOTIVATION AND HOMEOSTASIS

Motivation, which literally means “to set in motion,” refers to the set of factors that initiate, sustain, and direct behaviors. The need for the concept was prompted by psychologists’ inability to explain behavior solely in terms of outside stimuli. Assuming various kinds of motivation, such as hunger or achievement need, helped make sense of differing responses to the same environmental conditions.

Keep in mind, though, that *motivation is a concept psychologists have invented and imposed on behavior*. We should not expect to find a single “motivation center” in the brain or even a network whose primary function is motivation. The fact that we sometimes cannot distinguish motivation from other aspects of behavior, such as emotion, is evidence of how arbitrary the term can be. Still, it is a useful concept for organizing ideas about the sources of behavior.

After a brief overview of some of the ways psychologists have approached the problem of motivation, we will take a closer look at temperature regulation, thirst, and hunger as examples before taking up the topics of sexual behavior in Chapter 7 and emotion and aggression in Chapter 8.

Theoretical Approaches to Motivation

Greeks relied heavily on the concept of instinct in their attempts to explain human behavior. An **instinct** is a complex behavior that is automatic, unlearned, and unmodifiable and occurs in all the members of a species (Birney & Teevan, 1961). Migration and parental behavior are good examples of instinctive behaviors in animals. According to early instinct theorists, humans were guided by instincts, too, waging war because of an aggressive instinct, caring for their young because of a parental instinct, and so on. At first blush, these explanations sound meaningful. But if we say that a person is combative because of an aggressive instinct, we know little more about what makes the person fight than we did before; if we cannot then analyze the supposed aggressive instinct, we have simply dodged the explanation. Contemporary students of behavior have used stringent requirements of evidence to identify a few instincts in animals, such as homing and flight in birds. But most psychologists believe that in human evolution instincts have been for the most part replaced by learned behaviors.

Several theories have been proposed as a replacement to instinct. The first, drive theory, deals with motivation in terms of needs arising from physical conditions such as hunger, thirst, and body temperature. According to **drive theory**, the body maintains a condition of **homeostasis**, in which any particular system is in balance or equilibrium (C. L. Hull, 1951). Any departure from homeostasis, such as depletion of nutrients or a drop in temperature, produces an aroused condition, or **drive**, which impels the individual to engage in appropriate action, such as eating, drinking, or seeking warmth. **Incentive theory** recognizes that people are motivated by external stimuli, not just internal needs (Bolles, 1975). Incentives can meet a biological need (such as food, clothing, or mates) or can be things that are valuable to the individual (such as money or good grades). According to the theory, motivation is mostly geared toward seeking and acquiring external rewards, or incentives. Then again, sometimes we do things without either an obvious drive or an incentive. The first author’s wife once jumped out of an airplane for the thrill of plummeting toward the earth, only to be saved at the last minute by a flimsy parachute. Observations like this have led to the **arousal theory**, which states that people behave in ways that keep them at their preferred level of stimulation (Fiske & Maddi, 1961). Different people have different optimum levels of arousal, and some seem to have a need for varied experiences or the thrill of confronting danger (Zuckerman, 1971). This *sensation seeking* finds expression in anything from travel and unconventional dress to skydiving, drug use, risky behaviors, violence, and eating fugu (see Chapter 2). Incentives and arousal

share a common neural mechanism of increased release of dopamine in the brain, which can result in addiction (see Chapter 5).

? What do homeostasis and drive mean?

In the face of challenges to drive theory, psychologists have shifted their emphasis to drives as states of the brain rather than as conditions of the tissues (Stellar & Stellar, 1985). This approach nicely accommodates sexual behavior, which troubled drive theorists because it does not involve a tissue deficit. Even eating behavior is better understood as the result of a brain state. Hunger ordinarily occurs when a lack of nutrients in the body triggers activity in the brain. However, an incentive such as the smell of a steak on the grill can also cause hunger, apparently by activating the same brain mechanisms that tissue deficits do. In addition, the person feels satisfied and stops eating long before the nutrients have reached the deficient body cells. Similarly, if the brain is not "satisfied," it little matters how much the person has eaten. In other words, if the information that reserves are excessive fails to reach the brain or to have its usual effect there, the person may, like Christopher, eat to obesity and still feel hungry. In the following pages, we will look at the regulation of body temperature, fluid levels, and energy supply from the perspective of drive and homeostasis.

Simple Homeostatic Drives

To sustain life, a number of conditions, such as body temperature, fluid levels, and energy reserves, must be held within a fairly narrow range. Accomplishing that requires a *control system*. A mechanical control system that serves as a good analogy is a home heating and cooling system. Control systems have a **set point**, which is the point of homeostasis (or equilibrium) to which the system returns. For the heating and cooling system, the set point is the temperature selected on the thermostat. The result of a departure in the room temperature from the set point is analogous to a drive; the thermostat initiates an action, turning on the furnace or the air conditioner. Larger deviations from the system's set point trigger stronger drives to return to it. When the room temperature returns to the preset range, the system is "satisfied" in the technical sense of the word; homeostasis has been achieved, so the system goes into a neutral state until there is another departure from the set point.

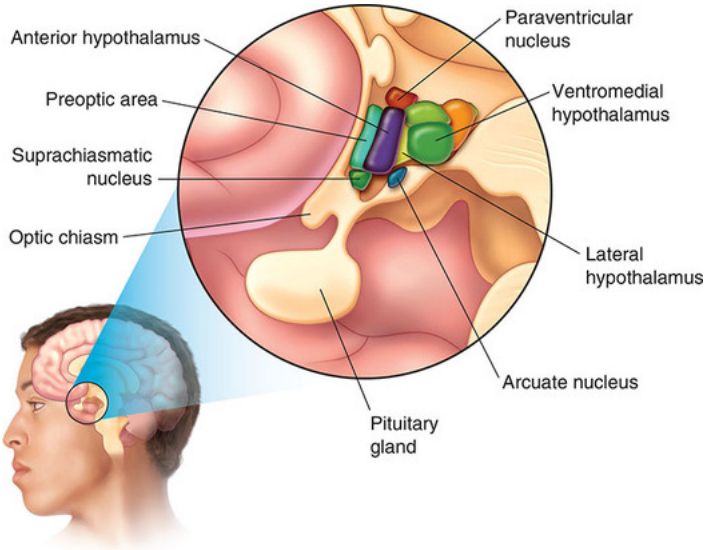
Temperature Regulation

Not only is the regulation of body temperature superficially similar to our thermostat analogy; it is almost as simple. All animals have to maintain internal temperature within certain limits to survive, and they operate more effectively within an even narrower range; this is their set point. How they respond to departures from homeostasis is much more variable than with the home heating and cooling system, however. *Ectothermic* animals, such as snakes and lizards, are unable to regulate their body temperature internally, so they adjust their temperature behaviorally by sunning themselves, finding shade, burrowing in the ground, and so on. *Endothermic* animals, which include mammals and birds, use some of the same strategies, such as building nests or houses, moving to warmer or cooler areas, and wearing clothing. However, endotherms are also able to use their energy reserves to maintain a nearly constant body temperature automatically. In hot weather, their temperature regulatory system reduces body heat by causing sweating, reduced metabolism, and dilation of peripheral blood vessels. In cold weather, it induces shivering, increased metabolism, and constriction of the peripheral blood vessels. To say that we make these adjustments because we *feel* hot or cold suggests that the responses are intentional behaviors, but, of course, that is not the case. So how do these behaviors occur?

? How is body temperature regulated?

In mammals, the major "thermostat" is located in the **preoptic area** of the hypothalamus, which contains separate warmth-sensitive and cold-sensitive cells (Figure 6.2; Nakashima, Pierau, Simon, & Hori, 1987). Some of these neurons

respond directly to the temperature of the blood flowing through the area; others receive input from temperature receptors in other parts of the body, including the skin. The preoptic area integrates information from these two sources and initiates temperature regulatory responses, such as panting, sweating, shivering, increasing or decreasing blood flow to the extremities, and building winter fat reserves as insulation against the cold (for a summary, see Morrison, 2016). We will be talking about several nuclei in the hypothalamus in this chapter, so you may want to refer to Figure 6.2 often.



Description

Figure 6.2 Selected Nuclei of the Hypothalamus.
The illustration shows only the right hypothalamus. The hypothalamus is a bilaterally symmetrical structure, which means that the left and right halves (separated by the third ventricle) are duplicates of each other. (The pituitary and optic chiasm have been identified for use as landmarks.)

Source: Nieuwenhuys, R., Voogd, J., & vanHuijzen, C. (1988). *The Human Central Nervous System* (3rd Rev. ed.). Berlin, Germany: Springer-Verlag.

Thirst

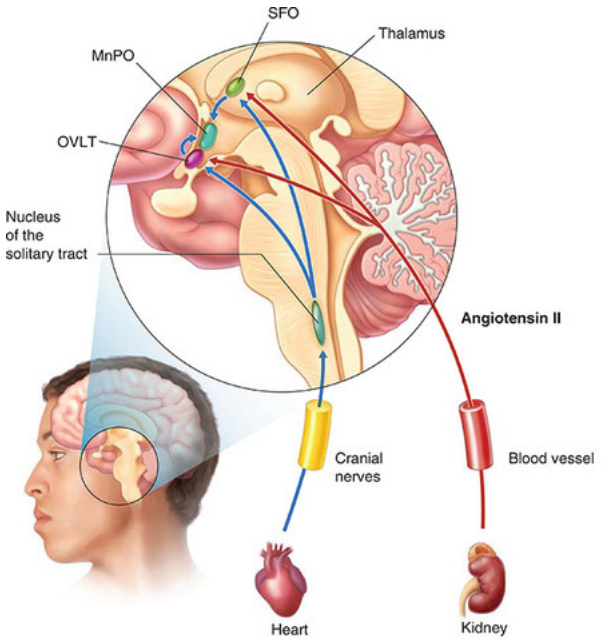
The body is about 70% water, so it seems obvious that maintaining water balance is critical to life. Water is needed to maintain the cells of the body, to keep the blood flowing through the veins and arteries, to transport nutrients, and to dispose of waste. You can live for weeks without eating but for only a few days without water, in part because of the constant loss through evaporation, urination, and defecation. The design of your nose, which could have been just a pair of nostrils on your face, is testimonial to the body's efforts to conserve water. As you breathe, you exhale valuable moisture; but as your breath passes through the much cooler passages of your nose, some of the moisture condenses and is reabsorbed.

It is also obvious that you drink when your mouth and throat feel dry, but a dry mouth and throat mostly influence *when* you drink, not *how much* you drink. There are two types of thirst generated by a drop in water content, one from inside the body's cells (*osmotic*) and the other from the blood (*hypovolemic*). Drinking remedies both kinds of deficits, but the fluid levels in the two compartments can vary independently, so the brain manages them separately. **Hypovolemic thirst** occurs when the blood volume drops due to a loss of extracellular water. This can be due to breathing, sweating, vomiting, urination, defecation, or a loss of blood. That is why you feel especially thirsty after you exercise, spend the day at the beach, or donate blood. (For relative

amounts of water loss at rest versus exercise, see Tam & Noakes, 2013, for a review.) **Osmotic thirst** occurs when the fluid content decreases inside the body's cells. This occurs along with hypovolemic thirst, but it occurs independently when the dissolved substances in the interstitial fluid surrounding the cells become more concentrated than the inside the cells. Water corrects this difference through osmosis, by leaving the cells and diluting the interstitial fluid. Eating a salty meal or drinking a beverage sweetened with sucrose (but not glucose, which readily passes through the cellular membrane) will result in osmotic thirst without hypovolemic thirst.

? How does the body regulate its water reserves?

Essential for sensing and regulating internal water balance are three small structures lying adjacent to the third ventricle: the **subfornical organ (SFO)**, the **organum vasculosum lamina terminalis (OVLT)**, and the **median preoptic nucleus (MnPO)**; see Figure 6.3; Augustine et al., 2018; Gizowski & Bourque, 2018; Verbalis, 2007; Zimmerman, Leib, & Knight, 2017). The SFO and the OVLT are *circumventricular organs*, which means they are outside the blood-brain barrier and therefore have direct access to the blood circulation. Some of their neurons function as *osmoreceptors*; these neurons indicate osmotic thirst by increased firing as their volume decreases due to fluid loss. Information from the SFO and OVLT is integrated in the MnPO, which provides the final output; stimulation of any of these three structures induces drinking within seconds, and lesioning the MnPO blocks drinking induced by stimulating SFO or OVLT.



Description

Figure 6.3 Thirst Control Signals and Brain Centers.
OVLT = organum vasculosum lamina terminalis; MnPO = median preoptic nucleus; SFO = subfornical organ.

Christina Wheeler/Body Scientific Intl.

Hypovolemic thirst is signaled in two ways: by stretch receptors (*baroreceptors*) located in arteries of the heart (Leib, Zimmerman, & Knight, 2016; Zimmerman et al., 2016) and by the peptide hormone angiotensin II. Information from the baroreceptors is conveyed by two cranial nerves (vagus and glossopharyngeal) to the nucleus of the solitary tract in the medulla (where it helps regulate blood pressure), then by way of the SFO and OVLT to the MnPO (McKinley et al., 2015; Zimmerman, Leib, & Knight, 2017). Lowered blood volume in the kidneys triggers release of the hormone

renin, which increases production of the hormone angiotensin II in the bloodstream. **Angiotensin II** informs the brain of the drop in blood volume by stimulating receptors in the SFO and OVLT. In both cases, drinking is then induced by the nearby MnPO.

So far, we've been talking about what *initiates* drinking; we still must ask how we know when to *stop* drinking. Based on what you've just learned, you might think that we stop drinking when the deficit is eliminated and the stimulatory signals subside. However, that takes 10 to 20 minutes to occur; if we continued to drink until the cellular need was satisfied, we'd be in danger of water intoxication, which would mean headache, confusion, alterations in behavior and personality, and possibly death. So how do we explain **satiety**, the satisfaction of appetite? Like humans, dogs drink an amount of water according to their cellular need and then stop (reviewed in G. Fink, Pfaff, & Levine, 2012). They will behave this way even when a tube in the stomach allows the water to drain out as quickly as it is ingested, so we can rule out the intestines as the source of the stop signal. Injecting water directly into the stomach doesn't inhibit drinking, so the stomach isn't involved, either. Researchers have concluded that the act of drinking itself signals the brain about the intake of water, and recent studies with mice have revealed the neural mechanism (Augustine et al., 2018; Zimmerman et al., 2016). Water intake is monitored by the MnPO; a subset of MnPO neurons fires during drinking and inhibits SFO neurons, beginning with the very first lick of water. Eating food or licking an empty water tube does not have this effect. Salty water inhibits the SFO as much as pure water, but this is reversed about a minute later as receptors detect the water's concentration.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- How do temperature regulation and thirst qualify as homeostatic drives?
- Receptors are able to do their jobs because they are specialized for specific types of stimuli. What are the specializations of the receptors we have seen so far?

HUNGER: A COMPLEX DRIVE

Although hunger can be described in terms of drive and homeostasis, just like temperature regulation and thirst, the differences almost overshadow the similarities. Hunger is more complicated in a variety of ways. Eating provides energy for activity, fuel for maintaining body temperature, and materials needed for tissue growth and repair. In addition, the set point is so variable that you might think there is none. This is not surprising, because the demands on our resources change with exercise, stress, growth, and so on. A changing set point is not unique to hunger, of course. For example, our temperature set point changes daily, decreasing during our normal sleep period (even if we fly east or west across several time zones or are awake during normal sleep time). It also increases during illness to produce a fever to kill invading organisms. What is unusual about hunger is that the set point can undergo dramatic and prolonged shifts, for instance, in obesity.

Another difference is that the needs in temperature regulation and thirst are unitary, whereas hunger involves the need for a variety of different and specific kinds of nutrients. Making choices about what foods to eat can be more difficult than simply knowing when to eat and when to stop eating.

Gustation: The Role of Taste

Selecting the right foods is no problem for some animals. Some *herbivores* (plant-eating animals) can get all the nutrients they need from a single source; koalas, for instance, eat only eucalyptus leaves, and giant pandas eat nothing but the shoots of

the bamboo plant. *Carnivores* (meat eaters) also have it rather easy; they achieve a balanced diet because their prey eats a balanced diet. We are *omnivores*; we can get the nutrients we need from a variety of plants and animals. Being able to eat almost anything is liberating but simultaneously a burden: We must distinguish among foods that may be nutritious, non-nutritious, or toxic, and we must vary our diet among several sources to meet all our nutritional requirements. Choosing the right foods and in the right amounts can be a real challenge.

It is possible that you plan your diet around nutritional guidelines, but probably you rely more on what you learned at the family table about which foods and what combinations of foods make an "appropriate" meal in your culture. Have you ever wondered where these traditions came from, or why they survive when each new generation seems to delight in defying society's other customs? Long before humans understood the need for vitamins, minerals, proteins, and carbohydrates, your ancestors were using a "wisdom of the body" to choose a reasonably balanced diet that ensured their survival and your existence. That wisdom is reflected in cultural food traditions, which usually provide a balanced diet (Rozin, 1976; Twiss, 2019), sometimes by dictating unattractive (to us) choices, such as grub worms or cow's blood. As you will see, the internal forces that guide our selection of a balanced diet are more automatic than the term *choice* usually suggests, but they are also subtle and easily overcome by the allure of modern processed foods, which emphasize taste over nutrition.

The simplest form of dietary selection involves distinguishing between foods that are safe and nutritious and those that are either useless or dangerous. This is where the sense of taste comes in. In humans, all taste experience appears to be the result of just five taste sensations: sour, sweet, bitter, salty, and the more recently discovered umami (Kurihara & Kashiwayanagi, 1998). The first four need no explanation; *umami* is a Japanese word meaning "pleasant savory taste," and the sensation is often described as "savory" or "meaty." These five sensations are called *primaries*; more complex taste sensations are made up of combinations of the primaries. There may be additional taste primaries; recent research, for example, has found evidence that we can distinguish the taste of starches (Lapis, Penner, & Lim, 2016) and fats (Besnard, Passilly-Degrace, & Khan, 2016).

It is easy to see why we have evolved taste receptors with these particular sensitivities, because they correspond closely to our dietary needs. We will readily eat foods that are sweet, which include fruits and carbohydrates. We also prefer foods that are a bit salty; salt provides the sodium and chloride ions needed for cellular functioning and for neural transmission. Mountain gorillas get 95% of their sodium by eating decaying wood—while avoiding similar wood with lower sodium content (Rothman, Van Soest, & Pell, 2006). Umami receptors aid in our selection of proteins; one type responds to amino acids, and two respond to glutamate (Chaudhari, Pereira, & Roper, 2009), which is found in meats, cheese, soy products, and the flavor enhancer monosodium glutamate (MSG). Just as we are attracted to useful foods by taste, we avoid others. Overly sour foods are likely to be spoiled, and bitter foods are likely to be toxic. You do not have to understand these relationships, much less think about them; they operate quietly, in the neural background.

Taste receptors are located on taste buds, which in turn are found on the surface of papillae; papillae are small bumps on the tongue and elsewhere in the mouth (Figure 6.4). These receptors are found all over the tongue; the "taste map" suggesting that different tastes are located at different locations on the tongue is a myth. It resulted from Harvard psychologist Edward G. Boring's (1942) misinterpretation of an earlier German study testing general taste sensitivity (Hänig, 1901) that then became a part of scientific folklore.

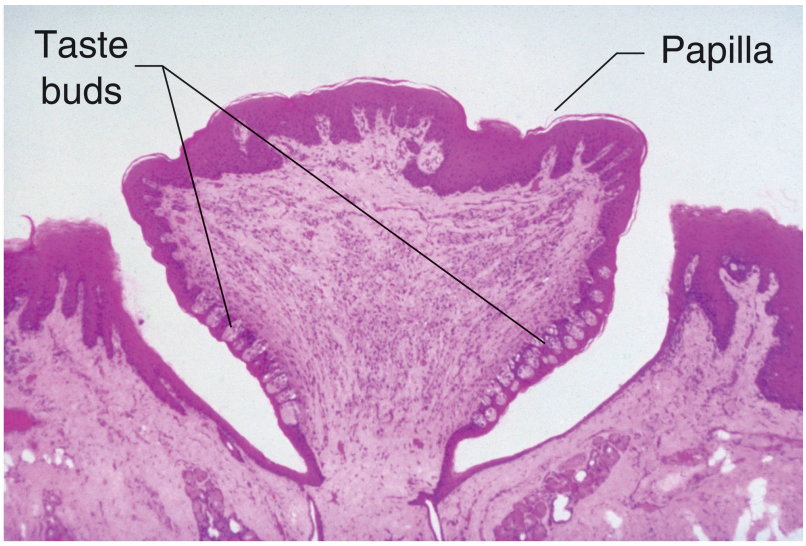


Figure 6.4 A Microscopic Photo of a Papilla With Taste Buds.
On the human tongue, there are between 2,000 and 8,000 taste buds.

Source: © Southern Illinois University/Science Source.

Axons from taste neurons travel through the thalamus to the primary gustatory (taste) area in the frontal lobes. But on their way, they pass through the nucleus of the solitary tract (NST) in the medulla, which we saw in Figure 6.3 in relation to drinking and will soon see plays a role in feeding behavior. Back in Chapter 2, you saw research indicating that taste neurons encode different taste stimuli as unique time patterns of impulses, but there is a more important way the system informs the brain of what we are tasting. Each of the primary taste stimuli is detected by receptors that are specialized for that stimulus; information from the different receptors travels to the brain via separate pathways to distinct areas in the insular cortex (Figure 6.5; X. Chen, Gabitto, Peng, Ryba, & Zuker, 2011; Schoenfeld et al., 2004). You will see in later chapters that other sensory systems exploit this *labeled line* coding of stimuli and that the brain combines primary sensations into more complex sensory experiences.

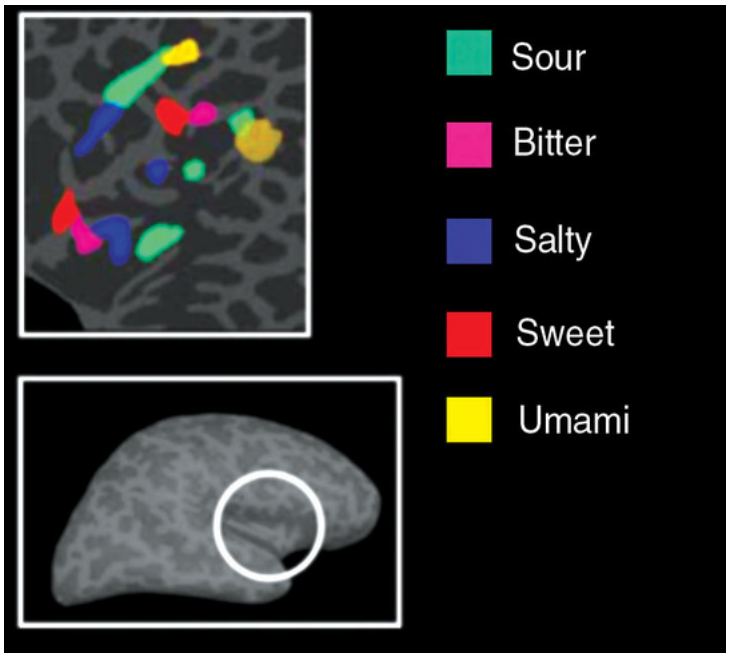


Figure 6.5 Localization of Taste Responses in the Gustatory Cortex.
The color-coded areas on this fMRI scan indicate where the insular cortex was activated as the subject tasted various liquids. The locations differed among subjects but were consistent over time for each subject. The location of the insular cortex is shown in the lower image.

Source: From "Functional Magnetic Resonance Tomography Correlates of Taste Perception in the Human Primary Taste Cortex," by M. A. Schoenfeld et al., 2004, *Neuroscience*, 127, 347-353. Used with permission from Elsevier.

Besides the nutritional and safety benefits we have already mentioned, the taste sense contributes to dietary selection in three additional ways: sensory-specific satiety, learned taste aversion, and learned taste preferences.

? In what ways does taste contribute to selection of a proper diet?

Sensory-Specific Satiety: Varying the Choices

When we were younger, many of us enjoyed trick-or-treating on Halloween night. Afterward, we would hide in our rooms and gorge ourselves on our favorite candies. But as we continued to eat, the pleasurable feelings declined until we couldn't stand to eat any more—the candy stopped tasting good. Barbara and Edmund Rolls call this experience sensory-specific satiety. **Sensory-specific satiety** means that the more an individual eats a particular food item, the less appealing the food becomes. Humans rate a food less favorably after they have consumed it, and they eat more if they are offered a variety of foods instead of a single food (Rolls, Rolls, Rowe, & Sweeney, 1981).

This effect sounds trivial, but it is not; sensory-specific satiety is the brain's way of encouraging you to vary your food choices, which is necessary for a varied diet. Back in the 1920s, Clara Davis (1928) allowed three newly weaned infants to choose all their meals from a tray of about 20 healthy foods. They usually selected only two or three foods at one meal and continued choosing the same foods for about a week. Then they would switch to another two or three foods for a similar period. Their self-selected diet was adequate to prevent any deficiencies from developing over a period of 6 months.

Sensory-specific satiety takes place in the NST. Place a little glucose (a simple sugar) on a rat's tongue, and it produces a neural response there. But if glucose is injected into the rat's bloodstream first, sugar placed on the tongue has less effect in the NST (Giza, Scott, & Vanderweele, 1992). The brain automatically motivates the rat—or you—to switch to a new flavor and a different nutrient.

Learned Taste Aversion: Avoiding Dangerous Foods

Learned taste aversion, the avoidance of foods associated with illness or poor nutrition, was discovered when researchers were studying bait shyness in rats. Farmers know that if they put out poisoned bait in the barn, they will kill a few rats at first, but the surviving rats will soon start avoiding the bait (thus the term *bait shyness*). Rats tend to eat only small amounts of any new food; unless it is very powerful, a small amount of the poison will make them ill instead of killing them, and they will avoid that food in the future. Learned aversion was studied in the laboratory by giving rats a specific food and then making them nauseous with a chemical such as lithium chloride or with a dose of X-ray radiation. Later, they refuse to eat that food (Garcia & Koelling, 1966). And when a juvenile blue jay eats a Monarch butterfly, the toxins inside the butterfly (gained through eating milkweed) trigger a vomit reflex; thereafter, the blue jay avoids eating anything resembling a monarch butterfly again (Figure 6.6).

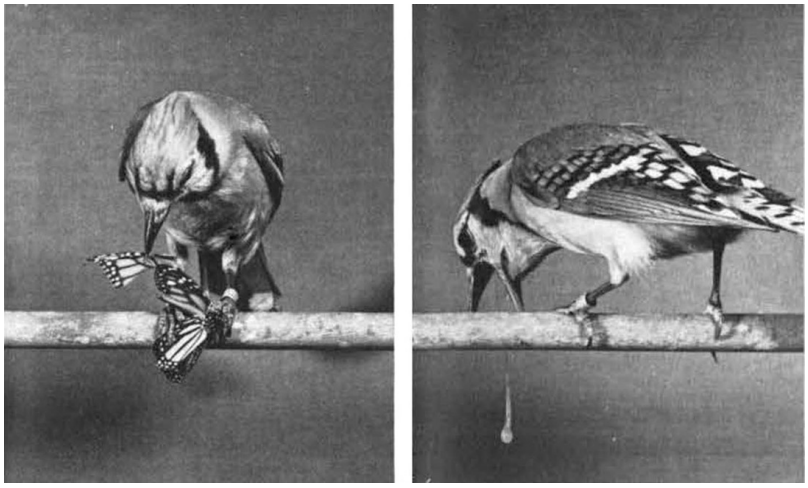


Figure 6.6 Learned Taste Aversion.
A young blue jay eats a monarch butterfly, which contains a toxin that triggers vomiting. The bird quickly associates the butterfly's colors with sickness and avoids eating similar butterflies from then on.

Source: Brower, L. P. 1969. Ecological Chemistry. Scientific American, 220(2), 22–29. Reprinted with permission.

Learned taste aversion helps wild animals and primitive-living humans avoid dangerous foods (see A Further Look). Modern-living humans experience learned taste aversions, too. In a study of people with strong aversions to particular foods, 89% could remember getting sick after eating the food, most often between the ages of 6 and 12 (Garb & Stunkard, 1974). However, in civilized settings, learned aversions have little value in identifying dangerous foods. Instead, we usually get sick following a meal because we left the food out of the refrigerator too long or because we happened to come down with stomach flu. Learned taste aversion appears to be one reason chemotherapy patients lose their appetite. Among children who were given a uniquely flavored ice cream before a chemo session, 79% later refused that flavor, compared with 33% of children receiving chemotherapy without the ice cream; the effect was just as strong 4 months later (I. L. Bernstein, 1978).

A Further Look:

Predator Control Through Learned Taste Aversion

The principles of classical conditioning and learned taste aversion have been put to practical use in an unlikely context: predator control. As a novel and humane (compared with extermination) means of controlling the frequency of wolves and coyotes killing sheep, Carl Gustavson and colleagues fed captive predators sheep carcasses laced with lithium chloride (see the photo), which made them sick. When they were placed in a pen with sheep, the wolves and coyotes then avoided the sheep instead of attacking them. One coyote threw up just from smelling a lamb, and two hesitant wolves were chased away by a lamb that turned on them (C. R. Gustavson, Garcia, Hankins, & Rusiniak, 1974; C. R. Gustavson, Kelly, Sweeney, & Garcia, 1976). Over a 3-year period, placing baited sheep meat on 10 ranches in Saskatchewan resulted in an 87% decrease in sheep predation by coyotes (C. R. Gustavson, Jowsey, & Milligan, 1982). These interventions also have benefits for conservation efforts because other endangered species (e.g., California condors, black-footed ferrets) are spared the traditional uses of traps and poisons that are intended for predators but sometimes kill other animals.

Learned taste aversion may not be very useful to modern humans for avoiding dangerous foods, but it may help us avoid non-nutritious ones. When rats are fed a diet that is deficient in a particular nutrient, such as thiamine (vitamin B), they start showing an aversion to their food; they eat less of it, and they spill the food from its container in spite of indications they are hungry, such as chewing on the wire sides of their cage (Rozin, 1967). Even after recovery from the deficit, the rats prefer to go hungry rather than eat the previously deficient food. But aversion to a nutrient-deficient food is just the first step toward selecting a nutritious diet.

Learned Taste Preferences: Selecting Nutritious Foods

Although rats, and presumably humans, can detect salt, sugars, and fat directly by their taste (M. Beck & Galef, 1989), they must *learn* to select the foods containing other necessary nutrients. This apparently requires the development of a **learned taste preference**, which is a preference not for the nutrient itself but for the flavor of a food that contains the nutrient. In an early study, rats were fed a diet deficient in one of three vitamins (thiamine, riboflavin, or pyridoxine); later they learned to prefer a food enriched with that vitamin, which was flavored distinctively by adding anise (which tastes like licorice). When the anise was switched to the vitamin-deficient food, the rats began eating that food instead (E. M. Scott & Verney, 1947). This type of learning requires pairing of a taste with some benefit, such as recovery from a dietary deficiency, and usually requires constant pairing over a period of several days (T. R. Scott, 2011). A diet-deficient rat enhances its chances of learning which foods are beneficial by eating a single food at a time (Rozin, 1969). (Notice how similar this is to the sampling behavior of Davis's infants, who were allowed to choose their own food.)

How much humans are able to make use of these abilities is unclear; we often choose an unhealthy diet over a healthy one. These bad selections may not be due so much to a lack of *ability* to make good choices as they are to the distraction of tasty, high-calorie foods that are not found in nature. Even rats have trouble selecting the foods that are good for them when the competing foods are flavored with cinnamon or cocoa (M. Beck & Galef, 1989), and they become obese when they are offered human junk food (Rolls, Rowe, & Turner, 1980). Wisdom of the body is inadequate in the face of the temptation of French fries and ice cream.

Now a caveat: You have most likely read that taste is largely a matter of smell, and perhaps you have even tested the idea by holding your nose while tasting familiar foods. In this context, it is important to distinguish between *taste*, which is the experience you get from your taste receptors, and *flavor*, which depends on a combination of taste, smell, texture, and temperature. Smell does have a significant effect; how much depends on the specific food and, to our knowledge, has never

actually been quantified (despite authoritative-sounding statements to the contrary). We will take up the topic of the sense of smell in Chapter 7.

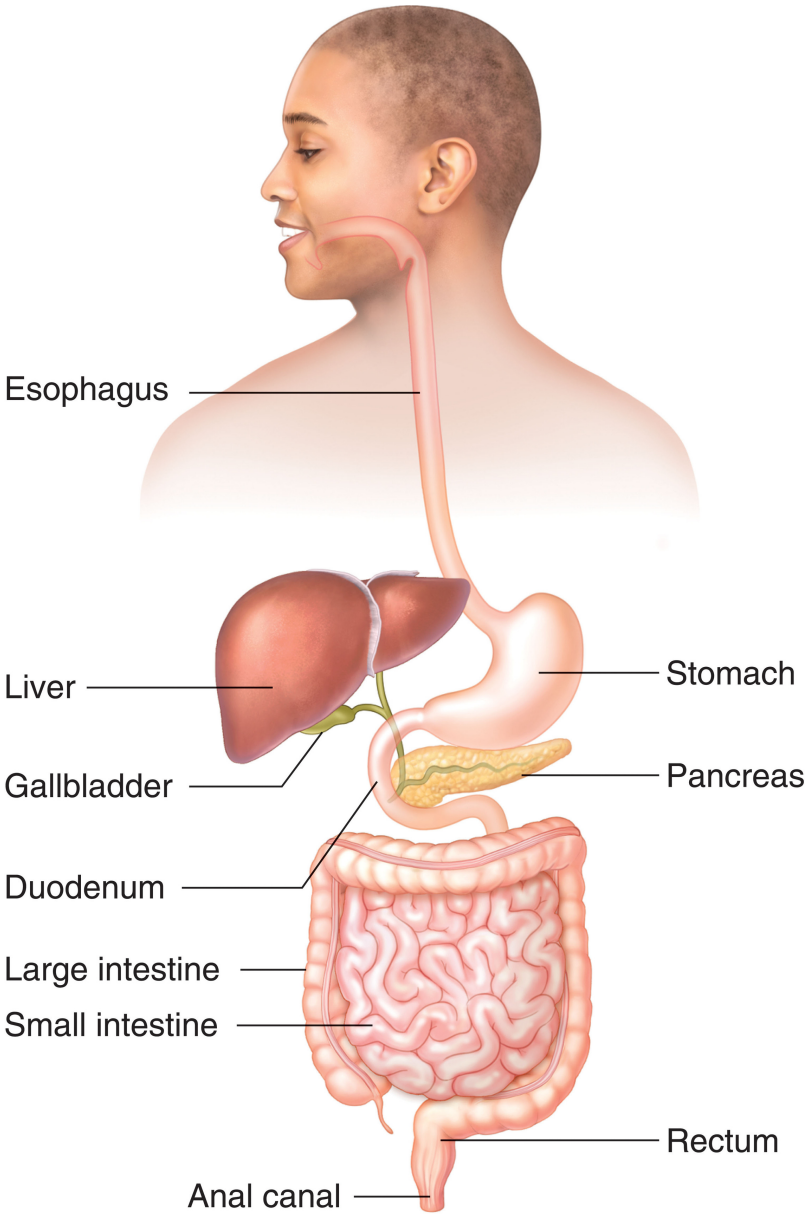
Digestion and the Two Phases of Metabolism

? What happens during the absorptive and fasting phases?

Here we confront the inadequacy in our thermostat analogy again. To maintain consistent temperature, the thermostat calls on the furnace to cycle on and off frequently. Some species of animals do behave like the home furnace; they eat low-calorie foods steadily, with only brief pauses, to provide the constant supply of nutrients the body needs. Other species eat large, calorie-dense meals and wait a long time before eating again; similarly, humans eat a few discrete meals and fast in between. Eating discrete meals leaves us free to do other things with our time, but it requires a complex system for storing nutrient reserves, allocating the reserves during the fasting periods, and monitoring the reserves to determine the timing and size of the next meal.

The Digestive Process

Digestion (the breakdown of complex molecules into their components) begins in the mouth, where food is ground fine and mixed with saliva. Saliva provides lubrication and contains an enzyme that starts the breakdown of carbohydrates. Digestion continues in the stomach as food is mixed with the gastric juices *hydrochloric acid* and *pepsin*. The partially processed food is then released gradually, so that the small intestine has time to do its job. (Figure 6.7 shows the organs of the digestive system.)



Description

Figure 6.7 The Digestive System.

The stomach provides another opportunity for screening toxic or spoiled food that gets past the taste test. If the food irritates the stomach lining sufficiently, the stomach responds by regurgitating the meal (like the blue jay in Figure 6.6). Some toxins don't irritate the stomach, and they make their way into the bloodstream. If so, a part of the brain often takes care of this problem; the **area postrema** is one of the places in the brain that is outside the blood-brain barrier, so toxins can activate it to induce vomiting. The result can be surprisingly forceful; projectile vomiting usually means that you've got hold of something really bad. On the other hand, college students have been known to incorporate this adaptive response into a drinking game called "boot tag," the details of which we will leave to your imagination.

Digestion occurs primarily in the small intestine, particularly the initial 25 centimeters of the small intestine called the **duodenum**. There, food is broken down into absorbable forms. Carbohydrates are metabolized into simple sugars, particularly

glucose. Proteins are converted to **amino acids**. Fats are transformed into **fatty acids** and **glycerol**, either in the intestine or in the liver. The products of digestion are absorbed through the intestinal wall into the blood and transported to the liver via the *hepatic portal vein*. Digestion requires the food to be in a semiliquid mix, and the body can ill afford to give up the fluid; the large intestine's primary job is absorbing the excess water.

This process is under the control of the autonomic nervous system, so digestion is affected by stress or excitement, as you probably well know. If too much acid is secreted into the stomach, you'll take your course exam with an upset stomach. If food moves too slowly through the system, constipation will be the result. Too fast, and there isn't time to remove the excess water, so you may be asking to leave the room in the middle of your exam to go to the bathroom. Because diarrhea causes the body to lose water, you may have to drink more liquids to avoid dehydration. You also lose electrolytes, compounds that provide the ions your neurons and other cells need, which is why your doctor may recommend a sports drink as the replacement liquid.

The Absorptive Phase

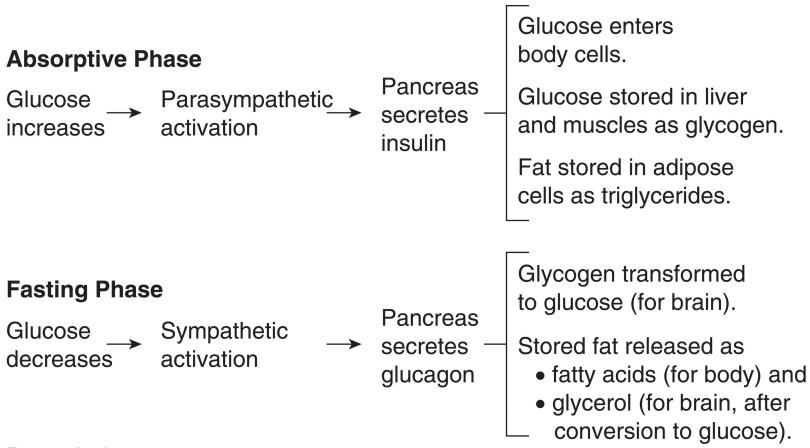
The feeding cycle is divided into two phases, the absorptive phase and the fasting phase. For a few hours following a meal, the body lives off the nutrients arriving from the digestive system; this period is called the **absorptive phase**. Following a meal, the blood level of glucose, our primary source of energy, rises. The brain detects the increased glucose and shifts the autonomic system from predominantly sympathetic activation to predominantly parasympathetic activity. As a result, the pancreas starts secreting **insulin**, a hormone that enables body cells to take up glucose for energy and certain cells to store excess nutrients. (Actually, because of conditioning, just the sight and smell of food is enough to trigger insulin secretion, increased salivation, and release of digestive fluids into the stomach. Remember the incentive theory?)

The cells contain *insulin receptors*, which activate transporters that carry glucose into the cells. **Diabetes** results when the pancreas is unable to produce enough insulin (type 1 diabetes) or the body's tissues are relatively unresponsive to insulin (type 2 diabetes). The diabetic's blood contains plenty of glucose following a meal, but due to insulin resistance (or lack of it), the cells of the body are unable to make use of it, and the diabetic is chronically hungry.

During the absorptive phase, the body is also busy storing some of the nutrients as a hedge against the upcoming period of fasting. Some of the glucose is converted into **glycogen** and stored in short-term reservoirs, mostly in the muscles and in the liver. Any remaining glucose is converted into fats and stored in fat cells, also known as *adipose tissue*. Fats arriving directly from the digestive system are stored there as well. Storage of both glucose and fat is under the control of insulin. After a small proportion of amino acids is used to construct proteins and peptides needed by the body, the rest is converted to fats and stored.

The Fasting Phase

Eventually the glucose level in the blood drops. Now the body must fall back on its energy stores, which is why this is called the **fasting phase**. The autonomic system shifts to sympathetic activity. The pancreas ceases secretion of insulin and starts secreting the hormone **glucagon**, which causes the liver and skeletal muscles to transform stored glycogen back into glucose. Because the insulin level is low now, this glucose is available only to the nervous system. To meet the rest of the body's needs, glucagon triggers the breakdown of stored fat into fatty acids and glycerol. The fatty acids are used by the muscles and organs, while the liver converts glycerol to more glucose for the brain. During starvation, muscle proteins can be broken down again into amino acids, which are converted into glucose by the liver. The two phases of metabolism are summarized in Figure 6.8.



Description

Figure 6.8 Summary of the Absorptive and Fasting Phases.

The Hypothalamic Circuitry of Hunger

The oscillations of eating and fasting and the shifts in metabolism that accompany them are orchestrated for the most part by four particularly important areas in the hypothalamus: the arcuate nucleus (ARC), the lateral hypothalamus (LH), the paraventricular nucleus (PVN), and the ventromedial hypothalamus (VMH; see Figure 6.2 again). The **arcuate nucleus (ARC)** is considered the master hypothalamic center for food intake control (Figure 6.9; Diéguez, Frühbeck, & López, 2009). The ARC integrates information it receives about nutrient levels with inputs from other hypothalamic areas and sends its output to all the hypothalamic nuclei, particularly the LH and the PVN. The extent of the ARC's control is suggested by its variety of neurons and transmitters. **NPY/AgRP neurons** increase eating and reduce metabolism by releasing the neuromodulators **neuropeptide Y (NPY)**, agouti-related protein (AgRP), and the neurotransmitter GABA; all these increase eating (Anderman & Lowell, 2017; Sternson & Eiselt, 2017), and NPY is involved in conserving energy as well. **Proopiomelanocortin (POMC) neurons** release POMC that activates the satiety neurons and decreases eating. A third type of neuron also activates the satiety neurons and reduces food intake, by releasing the excitatory neurotransmitter glutamate (Fenselau et al., 2017). AgRP neurons initiate voracious eating within minutes, but they reduce their activity as soon as food becomes available, with 96% decreasing activity just at the sight of food. This suggests that those neurons are involved in food seeking rather than food consumption (Fenselau et al., 2017; Sternson & Eiselt, 2017). Rats that receive NPY injections in the PVN double their rate of eating and increase their rate of weight gain six-fold (B. G. Stanley, Kyrkouli, Lampert, & Leibowitz, 1986). The fact that their weight gain is three times greater than their increase in food intake attests to NPY's ability to reduce metabolism. POMC deficiency results in massive obesity, both in mice and in humans (Anderman & Lowell, 2017).

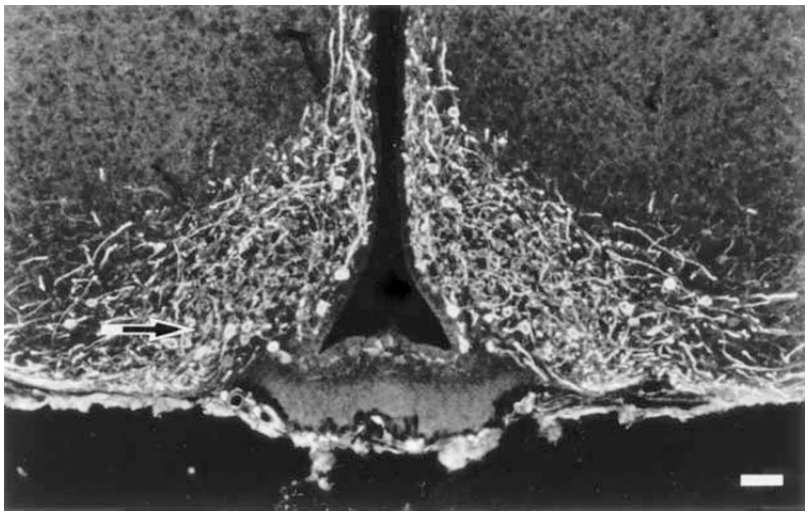


Figure 6.9 Immunohistochemical Labeling Highlights the ARC.

Source: From Figure 1 of "Hypothalamic and Vagal Neuropeptide Circuitries Regulating Food Intake," by C. Broberger & T. Hokfelt, 2001, *Physiology and Behavior*, 74, p. 670. Used with permission from Elsevier.

The **lateral hypothalamus (LH)** initiates eating and controls several aspects of feeding behavior as well as metabolic responses. It controls chewing and swallowing, salivation, gastric juice secretion, insulin production, and cortical arousal, which likely increases locomotion and the possibility of encountering food (Currie & Coscina, 1996; Saper, Chou, & Elmquist, 2002; Willie, Chemelli, Sinton, & Yanagisawa, 2001). Circuits in the LH also process the reward value and palatability of food, apparently promoting consumption of some foods over others (Sternson & Eiselt, 2017). When the LH was lesioned in animals, the result was reduced food intake, starvation, and eventually death (Diéguez et al., 2009). The LH receives input from the ARC, but it also has neurons that respond to hormonal and neural indicators of nutrient deficit; these release melanin-concentrating hormone and orexin (also known as hypocretin), both of which potently initiate eating (Anderman & Lowell, 2017; Gao & Horvath, 2007; Tsujino & Sakurai, 2009). Orexin neurons also excite NPY-only releasing neurons and inhibit POMC neurons in the ARC. The neuropeptide **orexin** not only increases eating but also produces arousal and increased wakefulness in response to food deprivation (Yamanaka et al., 2003). The term *orexin* is derived from *orexis*, the Greek word for "appetite." Any appetite stimulant—whether a drug, a visual or olfactory stimulus, or a naturally occurring neuropeptide hormone such as orexin or NPY—is referred to as *orexigenic*.

The **paraventricular nucleus (PVN)** regulates eating and metabolic processes such as body temperature, fat storage, and cellular metabolism (Broberger & Hökfelt, 2001; Sawchenko, 1998). POMC neurons from the ARC reduce eating by activating the PVN's satiety neurons; eating increases when the NPY/AgRP neurons inhibit the satiety neurons. The inhibitory NPY and GABA do so directly, while the excitatory AgRP antagonizes the output of POMC neurons (Anderman & Lowell, 2017; Sternson & Eiselt, 2017).

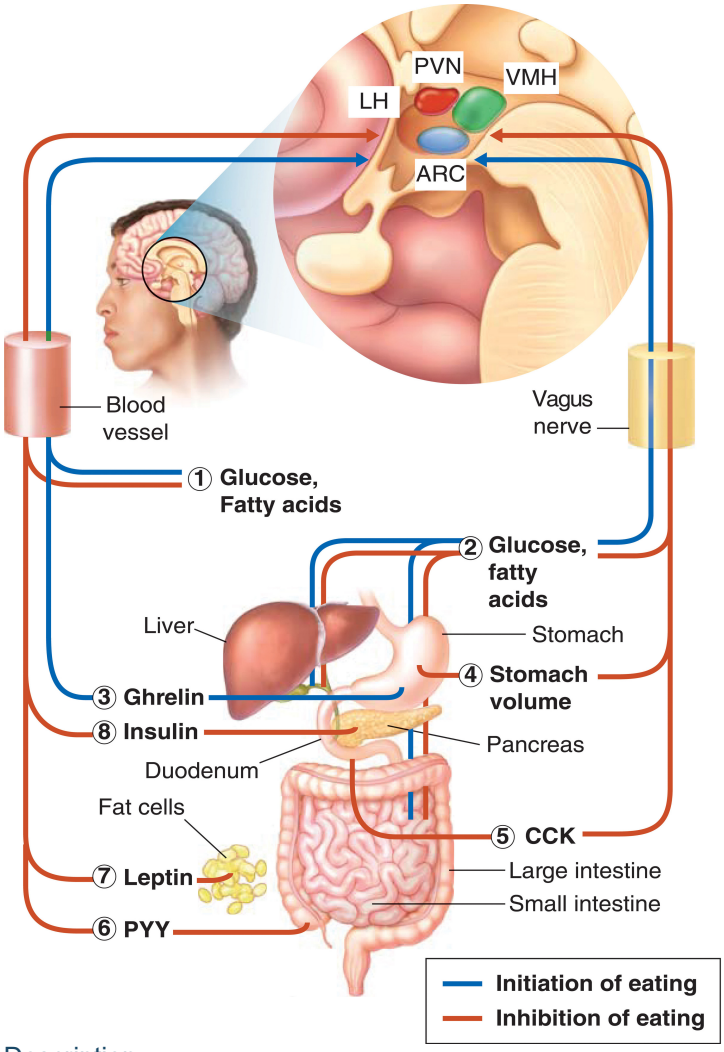
The **ventromedial hypothalamus (VMH)** produces satiety and increases metabolism. Lesions of the VMH make rats obese, due to reduced metabolism as well as increased appetite. Activation of VMH neurons by POMC neurons from the ARC reduces eating (B. M. King, 2006).

Signals That Initiate and Terminate Eating

What stimuli initiate eating?

We have to acknowledge what may seem obvious to you, that much of our eating depends on food availability, the food's taste and aroma, the time of day, and time elapsed since the last meal (Anderman & Lowell, 2017). In other words, we usually eat not because we have an energy or nutrient deficit but for pleasure and to prevent *future* deficit (S. C. Woods & Ramsay, 2007). All this masks the fact that, in the background, our brains are constantly monitoring the nutrients in our digestive and circulatory systems and our stored energy reserves and adjusting our food consumption accordingly.

Nearly all the body's energy comes from glucose and lipids (a subgroup of fats). When levels of circulating glucose or fatty acids are low, the effect is orexigenic, and high levels reduce eating. Glucose and fatty acids are transported across the blood-brain barrier, where they are detected by receptors on neurons in the ARC, LH, and VMH (Figure 6.10, Point 1; LeFoll, Irani, Magnan, Dunn-Meynell, & Levin, 2009; Verbene, Sabetghadam, & Korim, 2014). However, most monitoring of nutrients goes on in the periphery. In the case of glucose and fatty acids, receptors are located on branches of the vagus nerve in the small intestine and in the hepatic portal vein near the liver (Figure 6.10, Point 2; Darling et al., 2014; Verbene et al., 2014). The vagus nerve carries the information to the hypothalamus, where the ARC, LH, and VMH monitor glucose levels and the VMH also registers fatty acid levels (Verbene et al., 2014; Yi, la Fleur, Fliers, & Kalsbeek, 2010).



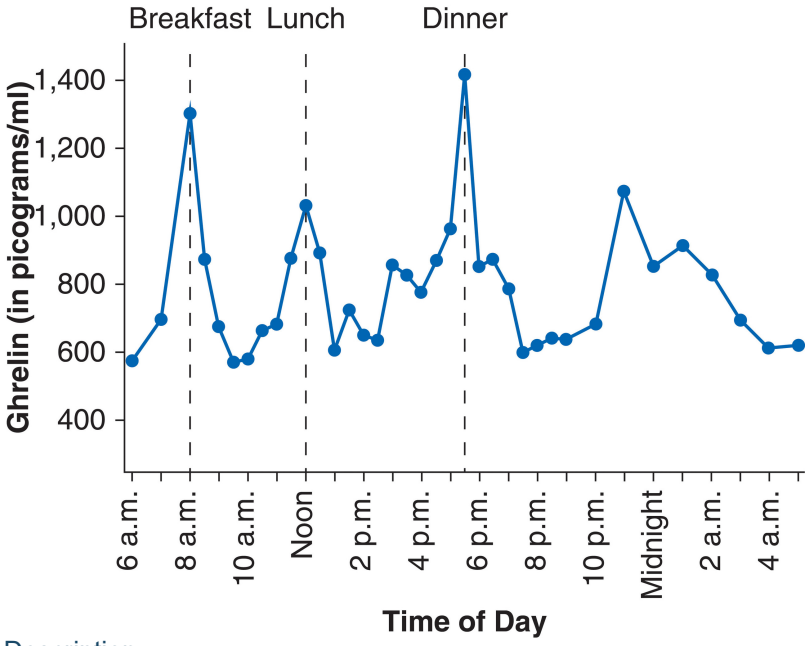
Description

Figure 6.10 Hunger Control Signals and Brain Centers.

Note: PVN = paraventricular nucleus; LH = lateral hypothalamus; ARC = arcuate nucleus; NST = nucleus of the solitary tract; PYY = Peptide YY3-36; CCK = cholecystokinin.

Carolina Hrejsa/Body Scientific Intl.

However, most of the brain's information about nutrient levels comes from hormones generated in the digestive system or by fat cells. One hormone is so intimately linked with eating that it has been called the *hunger hormone*. **Ghrelin** is an orexigenic peptide hormone that is synthesized in the stomach and released into the bloodstream during fasting (Figure 6.10, Point 3). As a neuropeptide hormone, it acts as a neurotransmitter; it crosses the blood-brain barrier and enters the ARC, where it activates receptors on AgRP neurons and increases NPY release (Gao & Horvath, 2007; Yamanaka et al., 2003). Ghrelin not only increases food intake; it also stimulates growth hormone release, participates in glucose and lipid metabolism, and regulates gastric motility (Yin, Li, & Zhang, 2014). Ghrelin secretion anticipates feeding; in humans, levels rise almost 80% before each meal and drop sharply within an hour after eating (Figure 6.11; Cummings et al., 2001). Ghrelin is the hormone we mentioned that partially accounts for the uncontrollable appetite of people like Christopher; it is 2.5 times higher in individuals with Prader-Willi syndrome than in lean controls and 4.5 times higher than the depressed levels found in equally obese individuals without the syndrome (Cummings et al., 2002).



Description

Figure 6.11 Ghrelin Levels in a Human Over a 24-Hour Period.
Notice that the ghrelin level started rising just before, and peaked at, the customary mealtimes.

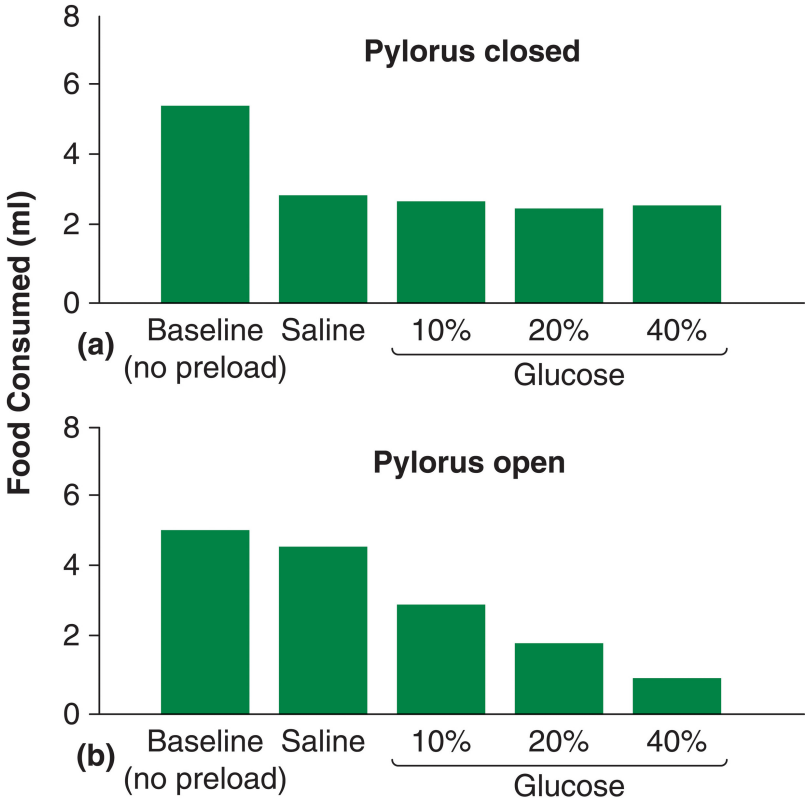
Source: From "A Preprandial Rise in Plasma Ghrelin Levels Suggests a Role in Meal Initiation in Humans," by D. E. Cummings et al., *Diabetes*, 50, (2001), p. 1716, fig. 2A. © 2001 American Diabetes Association.

? What stimuli terminate eating?

Just as with drinking, there must be a satiety mechanism that ends a meal well before nutrients reach the tissues. It might seem obvious that we stop eating when we feel "full," and that answer is partly right. R. J. Phillips and Powley (1996) found that when liquids infused into the stomach are blocked from passing into the intestines by a small inflatable cuff, saline is just as effective as glucose at reducing the amount of food rats eat a half hour later. The distension of the stomach activates

stretch receptors, which send a signal by way of the vagus nerve to the ventromedial hypothalamus (see Figure 6.10, Point 4; Spetter, de Graaf, Mars, Viergever, & Smeets, 2014; Sun, Tang, Zhang, & Chen, 2006). But a full stomach cannot produce long-term satiation by itself; otherwise, drinking water would satisfy us. Humans and other animals also adjust the amount of food they eat according to the food's nutritional value.

To a small extent, this involves oral factors and learning from past experience with the food. A high-calorie soup produces more hunger reduction if it is drunk than if it is infused directly into the stomach, and high-calorie drinks are immediately more satisfying than non-caloric drinks (French & Cecil, 2001). However, optimal satiation requires the interaction of mouth, stomach, and intestinal factors. When Phillips and Powley opened the cuff so that the stomach's contents could flow into the intestines, glucose was more effective at reducing subsequent eating, and higher concentrations of the glucose had a greater effect (Figure 6.12). The stomach and intestines release a variety of peptide hormones in response to food; different peptides are released in response to carbohydrates, fats, proteins, or mixtures of these nutrients. Some of these induce the pancreas, liver, and gallbladder to secrete the appropriate enzymes into the duodenum to digest the specific nutrient, but at least some of them inform the brain as to which nutrient needs are being met (S. C. Woods, 2004).



Description

Figure 6.12 Effect of Nutrient Concentration on Later Meal Size.
In all trials except the baseline, the stomach was preloaded with 5 milliliters of saline or glucose solution before the subject was offered a glucose solution to drink. The connection between the stomach and small intestine (the pylorus) could be closed by inflating a small cuff. (a) With the pylorus closed, nutrient value made no difference. (b) With the pylorus open, the amount consumed diminished as nutrient values increased.

Source: Adapted from "Gastric Volume Rather Than Nutrient Content Inhibits Food Intake," by R. J. Phillips and T. L. Powley, *American Journal of Physiology*, 271, pp. R766–R799. © 1996 American Physiological Society. Used with permission.

The best known of these satiety signals, the peptide hormone **cholecystokinin (CCK)**, is released by the stomach and small intestine as food passes into the duodenum. It limits meal size and aids digestion through the release of bile and enzymes. CCK stimulates receptors on the vagus nerve; as Point 5 in Figure 6.10 indicates, the vagus conveys the signal to the PVN (Anderman & Lowell, 2017). When researchers injected CCK into the bloodstream of obese humans, they ate less at the next meal (Pi-Sunyer, Kissileff, Thornton, & Smith, 1982). However, don't look for CCK to appear on the market as a weight-loss drug. Although rats given CCK eat smaller meals, they eat more often and maintain their weight (West, Fey, & Woods, 1984). This means that CCK's role is limited to meal size; there must be other controls that exert a more long-term effect.

Long-Term Controls

Peptide YY 3-36 (PYY) is a peptide hormone released in the intestines in response to food, which suppresses appetite over a longer period of time. PYY is carried by the bloodstream to the ARC, where it inhibits NPY-releasing neurons (see Figure 6.10, Point 6; Batterham et al., 2002). Unlike CCK, PYY's nonneural route to the brain means that its action is too slow to limit the current meal; instead, it decreases caloric intake by about one third over the following 12 hours.

? What are the signals for controlling body weight?

Over even longer periods, humans and animals regulate their eating behavior by monitoring their body weight or, more precisely, their body fat. But how they sense their fat level has not always been clear. In 1952, G. R. Hervey surgically joined pairs of rats so that they shared a very small amount of blood circulation; animals joined like this are called *parabiotic*. Then Hervey operated on one member of each pair to destroy the VMH; such lesions cause an animal to become obese, sometimes tripling in weight (Figure 6.13). Hervey's lesioned rats overate and became obese as expected, but their unoperated pairmates ate much less and lost weight. In fact, in two of the pairs, the lean rat starved to death. The message was clear: The obese rat was producing a blood-borne signal that suppressed eating in the other rat, a signal to which the brain-damaged obese rat was insensitive.

Figure 6.13 A Rat With a Lesioned Ventromedial Hypothalamus (VMH).

Source: Neal Miller, Yale University.

What that signal was remained a mystery until almost a half century later, when researchers discovered that fat cells secrete a peptide hormone called **leptin** that inhibits eating (Figure 6.10, Point 7). The amount of leptin in the blood is proportional to body fat; it is about four times higher in obese than non-obese individuals (Considine et al., 1996), which suggests that obese individuals are resistant to leptin. Leptin reduces meal size, but, unlike CCK, it also reduces total daily intake, resulting in weight loss (Anderman & Lowell, 2017).

The level of circulating insulin also is proportional to the size of fat reserves (M. W. Schwartz & Seeley, 1997) and provides a similar function. Together, leptin and insulin put the brakes on feeding in the ARC, again by activating POMC neurons and inhibiting NPY release (Figure 6.10, Point 8; Anderman & Lowell, 2017; Moran & Ladenheim, 2016). We now understand that when Hervey destroyed the VMH in rats, he also severed fibers passing through it and disconnected the ARC from the PVN (see Figure 6.2 again to see how this could happen).

Table 6.1 summarizes the factors that influence hunger and feeding that we have just covered (numbered to correspond to Figure 6.10). A Further Look makes the point that these pathways respond to more than just energy needs.

Table 6.1
Note: Numbers refer to items in Figure 6.10 and their descriptions in the text.

A Further Look:

TABLE 6.1 Summary of Feeding Signals.

STIMULUS	PATHWAY AND ACTION
Initiate eating	
1. Glucose and fatty acids (nutrients)	Low levels in the circulatory system are detected by receptors in the arcuate nucleus (ARC), lateral hypothalamus (LH), and ventromedial hypothalamus (VMH) to increase eating. High levels reduce eating.
2. Glucose and fatty acids (nutrients)	Receptors are located on the vagus nerve; low levels cause the ARC, LH, and VMH to increase eating. High levels reduce eating.
3. Ghrelin (peptide hormone)	Ghrelin is released by the stomach during fasting; it circulates in the bloodstream to the ARC, where it activates AgRP neurons to release neuropeptide Y (NPY).
Terminate eating	
4. Stomach volume (mechanical)	Stretch receptors send a signal about stomach volume via the vagus nerve to the nucleus of the solitary tract.
5. Cholecystokinin (CCK; peptide hormone)	CCK is released by the stomach and small intestine; it is detected by the vagus nerve, which activates inhibitory neurons in the PVN.
Long-term control	
6. Peptide YY3-36 (PYY)	PYY is released by the intestines and carried in the bloodstream to the ARC, where it inhibits NPY release.
7. Leptin	Leptin is released by fat cells and carried in the bloodstream to the ARC; it inhibits NPY release and activates POMC neurons.
8. Insulin	Insulin is released by the pancreas and travels in the bloodstream to the ARC; it inhibits NPY release and activates POMC neurons.

Note: Numbers refer to items in Figure 6.10 and their descriptions in the text.

How Nicotine and Marijuana Affect Appetite

People often say they can't stop smoking because it keeps their weight down, while some cancer and AIDS patients smoke marijuana to keep their weight up. Why these strategies work demonstrates just how complex our energy-regulating system is.

Researchers at Yale and Baylor Colleges of Medicine traced nicotine's appetite-suppressing effects to a subvariety of nicotinic acetylcholine receptor in the ARC, called a3β4 (Mineur et al., 2011). When nicotine stimulates these receptors, POMC neurons are activated and curtail appetite (Picciotto, 2013). Mice given a drug that targets a3β4 ate half as much as untreated mice in the next 2 hours, and over a month, their body fat dropped 15% to 20%. Areas important in hunger and feeding—the ARC, the PVN, and the VMH—also have an abundance of cannabinoid receptors, whose activation induces feeding (M. Koch et al., 2015). Injecting anandamide or THC into these areas caused satiated mice to resume eating (Di Marzo, Ligresti, & Cristino, 2009). In human volunteers, smoking marijuana cigarettes produced hunger-inducing increases in ghrelin levels and decreases in PYY.

There are several reasons for not smoking tobacco or marijuana, but understanding which cannabinoid and nicotinic receptors affect appetite should enable pharmaceutical researchers to develop safer substitutes; for example, there are already alternative ways of administering THC, such as with inhalers. Targeting the nicotinic and cannabinoid receptors might not be the best approaches to weight control, but the problems have been so daunting that researchers are always looking for new solutions.

Until now, we have been considering the ideal situation, the regulation of feeding and weight when all goes well. But as you are well aware, people eat too much, they eat the wrong kinds of foods, or they eat too little. As we will see, these behaviors are not just personal preferences or inconvenient quirks of behavior; too often, they are health-threatening disorders.

Concept Check

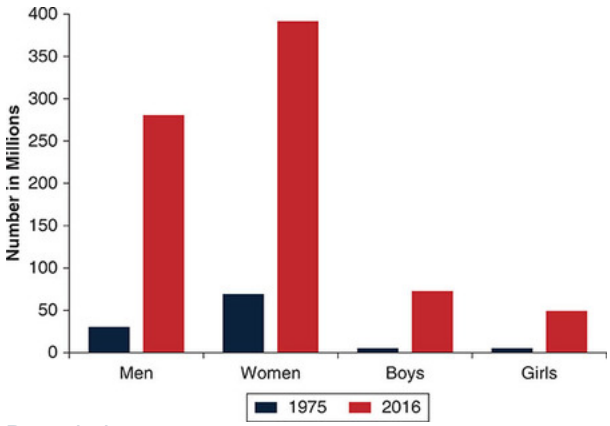
Take a Minute to Check Your Knowledge and Understanding

- What is the advantage of the ability to access stored nutrients between meals?
- How important are feeling "empty" and feeling "full" in the regulation of eating? Explain.

- You have lost weight during a long illness, and now you are ravenous. What are your likely levels of glucose, fatty acids, ghrelin, insulin, and leptin?

OBESITY

Between 1975 and 2016, the worldwide numbers of obese individuals increased nine-fold in men and nearly six-fold in women. Children's rates are lower, but they increased just as dramatically (Figure 6.14; NCD Risk Factor Collaboration, 2017). In developed countries, the picture is staggering. In the United States, for example, the obesity rate is 40% for adults, 21% among adolescents, and 18% for children (Hales, Carroll, Fryar, & Ogden, 2017). The number of people who are overfed and overweight now exceeds the number who are hungry and underweight, leading the World Health Organization (WHO) to declare obesity a global epidemic (NCD Risk Factor Collaboration, 2016). There are many causes of obesity, but an abundance of food has also been accompanied by the availability of high-calorie junk food. Although the percentage of underweight people has decreased globally, the numbers of people who are *malnourished* has been reported as almost double the numbers who are *undernourished* (G. Gardner & Halweil, 2000).

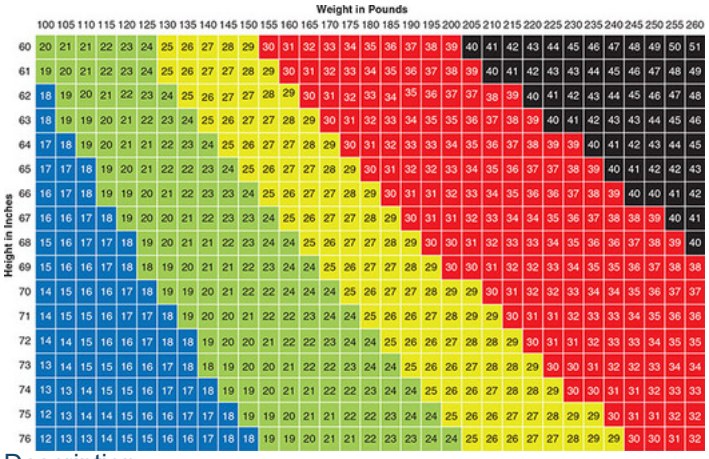


Description

Figure 6.14 Global Numbers of Obese Individuals, 1975–2016.

Source: Based on data from NCD Risk Factor Collaboration, 2017.

Most researchers use the WHO's BMI calculation to quantify leanness and obesity. **Body mass index (BMI)** is calculated by dividing the person's weight in kilograms by the squared height in meters. If you don't know your measurements in metric units, you can use the table in Figure 6.15, which also shows the WHO categories based on health risks. BMI is a rough measure, and it can be inaccurate in some individuals; because muscle is heavier than fat, a healthy, bulked-up athlete will have a high BMI score. A more complete analysis would include a body fat measure and the waist-to-hip ratio. Fat happens to be a very poor conductor of electricity; some bathroom scales measure body fat by applying a small electric current to the feet to measure resistance and, therefore, the percentage of body fat.



Description

Figure 6.15 Body Mass Index Calculation Chart.
Below 18.5 (blue): underweight; 18.5 to < 25 (green): normal; 25.0 to < 30 (yellow): overweight; 30 to < 40 (red): obese; 40 and above (black): extreme obesity.

Source: Adapted from "Obesity: How Big a Problem?" by I. Wickelgren, Science, 280, pp. 1364–1367. Copyright 1998 American Association for the Advancement of Science.

Note: Each box indicates the BMI calculated using the Centers for Disease Control and Prevention formula: BMI = 703 × weight (lbs) / [height (in)]^2.

Obesity is most important because of its health risks. It is a major risk factor for diabetes, and as overweight and obesity increase, so does the incidence of diabetes. Rates of the disease more than doubled from 1990 to 2008, but in recent years, the rate of increase has leveled off (Geiss et al., 2014). An estimated 30.3 million people, or 9.4% of the population, have diabetes in the United States (Centers for Disease Control and Prevention, 2017). Being overweight also increases the likelihood of high blood pressure, heart disease, stroke, and colon cancer (Field et al., 2001; Must et al., 1999). Obesity is also linked to cognitive decline and risk for Alzheimer's disease. Researchers have found cortical thinning and loss of temporal lobe volume in overweight and obese individuals (Caunca et al., 2019; Gustafson, Lissner, Bengtsson, Björkelund, & Skoog, 2004), possibly due to impaired blood flow to the brain or excess release of the stress hormone cortisol. The financial cost of obesity in the United States may be as high as $305 billion annually; according to one analysis, medical costs account for $190 billion, workplace absenteeism and reduced productivity cost $65 billion, and obesity-related health education adds another $50 billion (Blake, 2014). At the personal level, obesity costs the individual an additional $3,429 every year for health care (Biener, Cawley, & Meyerhoefer, 2017). It is no wonder that researchers are open to even the most novel sources for treatments, such as the one described in A Further Look.

A Further Look:

Diabetes, the Duck-Billed Platypus, and the Cone Snail

Insulin is often used to regulate blood sugar level in people with diabetes; the gut hormone glucagon-like peptide-1 (GLP-1) is an attractive alternative because it increases insulin naturally, but it is degraded too rapidly to be useful as a diabetes treatment. Enter the platypus, an animal so strange looking that when scientists first saw one in 1799, they believed it was a fake cleverly sewn together from several animals. The male of the species produces GLP-1, too, not only in the gut but also in a painful venom that it delivers from spurs on its hind feet when fighting other males during mating season. To serve that function, the platypus has evolved a more stable

form of GLP-1, which is degraded by a different mechanism from the one in humans and would be more stable in the human body (Mills, 2018; Tsend-Ayush et al., 2016).

Another possible alternative to insulin is the venom of a species of marine cone snail (see Chapter 2). When the cone snail ejects the venom into the water, it immobilizes a fish so that the snail can devour it. The venom produces hypoglycemic shock, a physiological state in which extremely low blood sugar induces a mild sedation in its prey (Safavi-Hemani et al., 2015). The cone snail's type of insulin is fast acting, which makes it attractive for treating diabetes. It can bind to human insulin receptors, and recent research has shown that it reverses high blood sugar in fish and mouse models of the disease (Ahorukomeye et al., 2019).

In other words, the diabetic patient's unlikely future best friends could be a duck-billed, web-footed, egg-laying mammal and a venomous snail hiding in a deceptively beautiful shell, both from Australia.

Health declines mean more than reduced quality of life. For every 5-point increase in BMI over age 25, the risk of death increases by 31% (de Gonzalez et al., 2010); the result is a shortening of lifespan between 2 and 10 years, depending on the degree of overweight (Prospective Studies Collaboration, 2009). Between 1990 and 2008, there was a small decrease in life expectancy in the United States, marking the first time in a century that longevity had failed to increase (Olshansky et al., 2012). Between 2014 and 2017, health officials were stunned by an additional decrease of three tenths of a year (Devitt, 2018). The trend was largely attributed to drug overdose deaths and suicide, but studies have shown that obesity is also a major contributor, adding as many as 186,000 excess deaths per year (S. H. Preston, Vierboom, & Stokes, 2018; H. Xu, Cupples, Stokes, & Liu, 2018).

Just as obesity is detrimental to health, caloric restriction without malnutrition appears to be beneficial, even in people who aren't obese. As you would expect, limiting the number of calories by around 30% reduces cholesterol, triglycerides, and circulating levels of insulin and glucose, but it also lowers blood pressure and improves heart health and functioning (P. K. Stein et al., 2012; Trepanowski, Canale, Marshall, Kabir, & Bloomer, 2011). Feeding restriction increases the lifespan of rats and mice by 20% to 60% (Kennedy, Steffen, & Kaeberlein, 2007). The 40- to 50-year lifespan of laboratory monkeys makes extending the results to other primates difficult, but the handful of studies that have been conducted generally indicate that calorie restriction can reduce disease and extend life (Colman et al., 2014).

We'll have to wait a few more years to find out whether dietary restriction will extend the life of humans, but there is evidence that it can improve quality of life in the meantime. A 2-year study in which volunteers reduced their calorie intake by 12% resulted in improved general health, better sleep quality and duration, improved mood, tension reduction, and improved sexual drive and relationships (C. K. Martin et al., 2016). Calorie restriction mimetics are compounds that alter the functioning of the same genes that respond to calorie restriction; some of these have shown potential for reducing effects of aging and treating various diseases (Magalhães, Wuttke, Wood, Plank, & Vora, 2012).

The Myths of Obesity

? Is obesity due to a lack of willpower?

Because obesity is dangerous to the person's health as well as an occasion for social and career discrimination, it is important to ask why people become overweight and why obesity rates are rising so dramatically. Although the causes have been difficult to document, most authorities believe that the global increase in obesity has a simple explanation: People are eating more and richer foods and exercising less (J. O. Hill, Wyatt, Reed, & Peters, 2003). The cause of obesity seems straightforward enough, then: *Energy in* exceeds *energy out*, and the person gains weight. But we would miss the point entirely if we assumed that people become obese just because they cannot resist the temptation to overeat. Research has not supported the popular opinion that obesity is completely under voluntary control (Volkow & Wise, 2005) or

that it can be characterized simply as lack of impulse control, inability to delay gratification, or maladaptive eating style (Rodin, Schank, & Striegel-Moore, 1989). In fact, as we will see later, obesity has a number of features in common with drug addiction.

Another popular belief is that obese children learn overindulgence from their family. Obesity does run in families, and BMI and other measures are moderately related among family members. However, the evidence consistently points to genetic rather than environmental influences as more important (Grilo & Pogue-Geile, 1991). To the extent that environment does play a role, it is mostly from outside the family.

The Contributions of Heredity and Environment

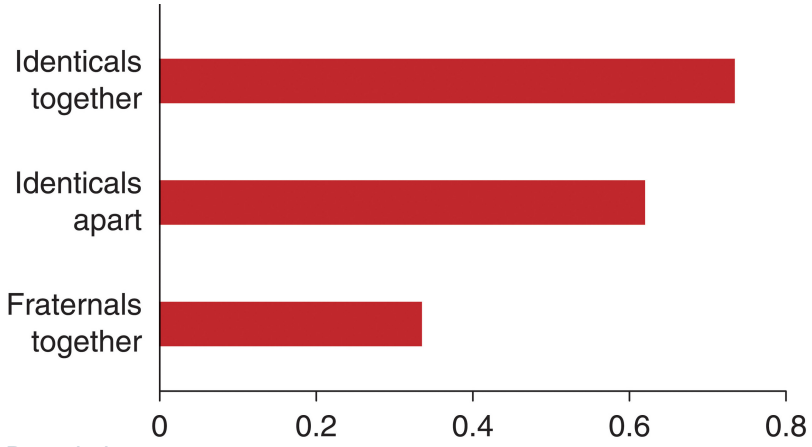
Two environmental influences on weight and obesity are obvious—diet and activity level. During the last three decades of the 20th century, advancing prosperity and improved agricultural production led to greater food availability, and per-capita calorie consumption increased by 1% or more per year in most areas of the world (S. Rosen, 1999). But this abundance turned out to be a mixed blessing, due to unhealthy dietary choices; for example, by the year 2000, half of calorie consumption in the United States consisted of carbohydrates, and fat made up another third (J. D. Wright, Kennedy-Stephenson, Wang, McDowell, & Johnson, 2004). This increased consumption added about 200 calories per day to the average U.S. diet (J. D. Wright et al., 2004), while decreasing energy demands on the job reduced daily energy expenditure by more than 100 calories (Church et al., 2011). As people drive rather than walk and spend more time on electronic devices and in front of televisions, activity levels are decreasing to the point that much of the world's population could be classified as sedentary (Ng & Popkin, 2012). Physical activity begins to decline in adolescence, and reduced physical activity during that time is a strong predictor of obesity at age 25 (Pietiläinen et al., 2008).

A less obvious influence is sleep deprivation. Over the last century, average sleep time has decreased from around 9 hours per night to 6 hours and 40 minutes, a loss of 35%. Adults who sleep less than 6 hours per night on workdays have a 41% obesity rate, compared with 28% for 8-hour sleepers, and each hour of lost sleep during adolescence increases the risk of obesity by 80% (reviewed in McAllister et al., 2009). Sleep loss reduces leptin levels and increases ghrelin secretion, both of which cause a craving for high-calorie foods (Greer, Goldstein, & Walker, 2013).

More surprising than the sleep connection is the possibility that some obesity is the result of infection. In one study, the presence of antibodies for four common viruses accounted for 9% of subjects' fat mass (Fernández-Real, Ferri, Vendrell, & Ricart, 2007). The Ad-36 virus is the most studied, with most studies linking Ad-36 infection to obesity in humans (Akheruzzaman, Hegde, & Dhurandhar, 2018). Infecting animals with the viruses increases glucose uptake by fat cells and makes the animals obese; this indicates that the viruses likely *cause* obesity in humans rather than being a result of it (McAllister et al., 2009). Bacteria also appear to play a role. Bacteria of the phylum *Firmicutes* apparently increase energy extraction from nutrients, while another phylum, *Bacteriodetes*, may have a protective function. In one study, obese children had a higher ratio of *Firmicutes* bacteria to *Bacteriodetes* (Bervoets et al., 2013). When researchers transferred gut bacteria from obese humans to mice that had no gut microbes of their own, the mice increased their body fat by 10%, even though they were eating the same amount of food as mice that received microbes from the human donors' lean twins (Ridaura et al., 2013). Later, cohousing the two groups of mice allowed them to eat each other's feces, which they have the unsavory habit of doing. As a result, *Bacteriodetes* invaded the intestines of the overweight mice, dominated the *Firmicutes* in number, and prevented the mice from gaining further weight. There has been only one small clinical trial that introduced gut microbes from a lean person into obese individuals; the procedure increased production of a bile acid that breaks down fats, but the volunteers did not lose weight (Saey, 2019).

? Is obesity hereditary?

Both adoption studies and twin studies demonstrate the influence of heredity on body weight. Adopted children show a moderate relationship with their biological parents' weights and BMIs, and little or no similarity to their adoptive parents (Grilo & Pogue-Geile, 1991). In a meta-analysis of several twin studies involving 75,000 individuals, correlations for BMI averaged .74 for identical twins and .32 for fraternal twins (Maes, Neale, & Eaves, 1997). Even when identical twins are reared apart, the correlation drops only to .62 (Grilo & Pogue-Geile, 1991), still almost double that for fraternal twins reared together (Figure 6.16). Across 88 twin studies, heritability of BMI varied from .47 to .90 (Elks et al., 2012). The authors attributed the variation to methodological differences, but others have pointed out that heritability of obesity can vary greatly across populations (W. Yang, Kelly, & He, 2007). Interestingly, the correlation between twins increased during childhood, likely due to increasing gene expression, and decreased through adulthood, possibly reflecting the individuals' exposure to differing environmental influences.



Description

Figure 6.16 Correlations of Body Mass Index Among Twins.
Notice that the correlation is higher for identical twins than for fraternal twins, even when the identicals are reared apart and the fraternals are reared together.

Source: Based on data from Grilo and Pogue-Geile (1991). The nature of environmental influences on weight and obesity: A behavior genetic anlaysis. *Psychological Bulletin*, 110, 520–537.

A half century ago, it was known that the so-called **obesity gene** on chromosome 6 and the **diabetes gene** on chromosome 4 cause obesity in mice. Mice that are homozygous for the recessive obesity gene (*ob/ob*) or the recessive diabetes gene (*db/db*) have the same symptoms: overeating, obesity, and susceptibility to diabetes (Figure 6.17). To find out how the two genes produced these symptoms, Daniel Coleman used parabiotic pairings of the two kinds of mice and normals (Figure 6.18; Coleman, 1973; Coleman & Hummel, 1969). When a *db/db* mouse was paired with either a normal mouse or an *ob/ob* mouse, the second mouse starved to death. This suggested to Coleman that the *db/db* mouse was producing a satiety signal that it was itself incapable of responding to. The *ob/ob* mouse had no effect on a normal mouse, but its own rate of weight gain slowed. Apparently the *ob/ob* mouse was sensitive to a satiety signal that it did not produce. But to test these interpretations, researchers would have to wait another 20 years, until the fat-generated satiety signal was identified as leptin. Injecting leptin into *ob/ob* mice reduced their weight 30% in just 2 weeks, while *db/db* mice were not affected by the injections (Halaas et al., 1995). We now understand that the *ob* gene encodes the production of leptin, and the *db* gene is responsible for the receptor.

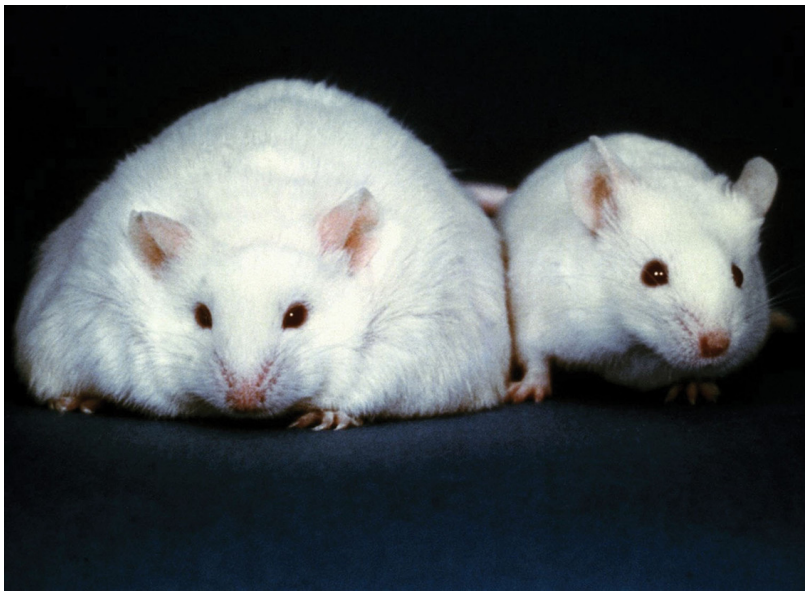
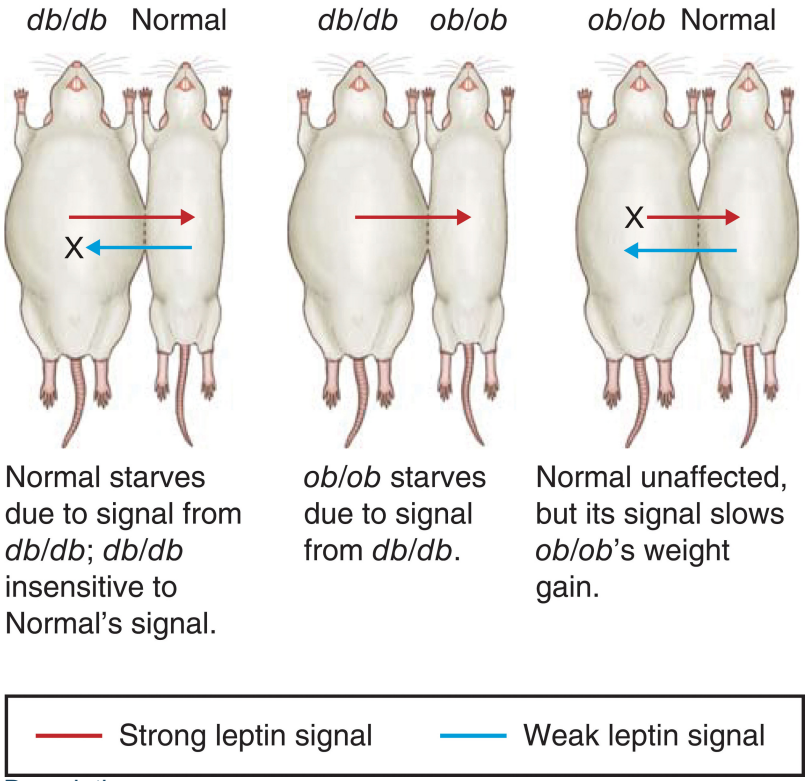


Figure 6.17 The Mouse on the Left is an *ob/ob* Mouse.

ORNL / Science Source



Description

Figure 6.18 Effects of Leptin on *db/db*, *ob/ob*, and Normal Mice.

Christina Lorenzo/Body Scientific Intl.

Those genes are rare in the population, however, and account for relatively few cases of obesity. By contrast, 16% of the population has two copies of the A allele of the

FTO (fat mass and obesity–associated) gene, and this increases their risk of obesity by nearly 70%; even a single copy ups the risk by 30% (Frayling et al., 2007). *FTO A* and other variants of *FTO* increase food intake by reducing leptin levels and receptor sensitivity and by increasing ghrelin levels and insulin sensitivity (Benedict et al., 2014; Heni et al., 2016; Stratigopoulos et al., 2014). The *MC4R* gene encodes for the MC4 receptor, which is involved in regulating appetite and energy expenditure; some of its variants add 12% to the risk for obesity in women (Loos et al., 2008) and account for 6% of cases of severe childhood obesity (Farooqi et al., 2003). Four variants of the *Mrap2* gene found in severely obese individuals apparently interfere with functioning of the MC4 receptor (Asai et al., 2013). All these mutations account for only a fraction of obesity cases, however. At least 67 gene locations have been linked to obesity (Choquet & Meyre, 2011), and additional candidates turn up regularly. This research reminds us that there are many paths to obesity, including increased appetite, diminished satiety, reduced metabolism, and increased fat storage; accordingly, obesity results from the contributions of many genes.

In a 2018 study, researchers identified cognitive and brain structural characteristics associated with weight increase and determined that several of these characteristics are genetic in origin (Vainik et al., 2018). In the cognitive realm, these include decreases in cognitive flexibility, visuospatial ability, and verbal memory and reduced ability to delay gratification. These deficits were accompanied by a thinner right prefrontal cortex, decreased volume in the hippocampal area, and increased volume in the left amygdala. The combination of characteristics suggests that people prone to obesity are more sensitive to visual food cues and less able to consider the consequences of succumbing to temptation.

Heritability measures leave room for significant environmental influence; indeed, we must recognize that the recent surge in obesity is due to nongenetic factors, such as diet and activity level. Even the tendency of overweight women to give birth to overweight babies cannot be attributed entirely to inheritance (M. H. Black, Sacks, Xiang, & Lawrence, 2013; Hochner et al., 2012); children born to women after they have lost weight through bariatric surgery are only one third as likely to be obese, compared with their siblings born before the surgery (J. Smith et al., 2009). The reason this discussion is occurring here is that environmental influences often work by altering gene activity. The term **epigenetic** refers to modifications to DNA that turn genes “on” or “off,” without changing the gene’s DNA sequence. One mechanism of epigenetic change is *methylation*, the attachment of molecules called methyl groups to a gene, which makes it more difficult for the gene to function. Methylation of the *RXRA* gene at birth, apparently caused by the mother’s low carbohydrate intake, accounts for more than 25% of variation in the offspring’s weight (Godfrey et al., 2011). Methylation of a gene that determines whether ingested fat is burned or stored has also been linked to obesity (Castellano-Castillo et al., 2019). Epigenetic alterations apparently contribute not only to weight gain but also to associated health problems, such as inflammation, diabetes, cardiovascular disease, and cancer.

You can see a graphic demonstration of the effects of methylation in Figure 6.19. Both mice have a mutation in the *agouti* gene, which is responsible for the agouti-related peptide mentioned earlier; the mutation produces obesity and an atypical yellow coat. But during pregnancy, the mother of the mouse on the right was fed supplements high in methyl groups (folic acid and vitamin B12); the resulting methylation downregulated the mutant gene (Waterland & Jirtle, 2003). But the most dramatic example comes from the Dutch *hunger winter* of 1944–1945, when Germany blockaded food shipments to western Holland and 20,000 people died from starvation. A study of young men whose mothers were exposed to famine during early pregnancy found that they were more often obese than unexposed control subjects (Ravelli, Stein, & Susser, 1976). More recent follow-up studies discovered the likely reason: In individuals exposed during early gestation, several genes that control prenatal growth showed increases or decreases in methylation, the remnants of epigenetic changes that occurred six decades earlier (Tobi et al., 2009; Tobi et al., 2012). Hunger winter offspring also had twice the typical rate of schizophrenia (Susser et al., 1996). In the following chapters, we will see growing evidence of the role of epigenetic influences on our lives and our well-being. While some epigenetic changes contribute to weight gain, others result from obesity, and they are the topic of A Further Look.

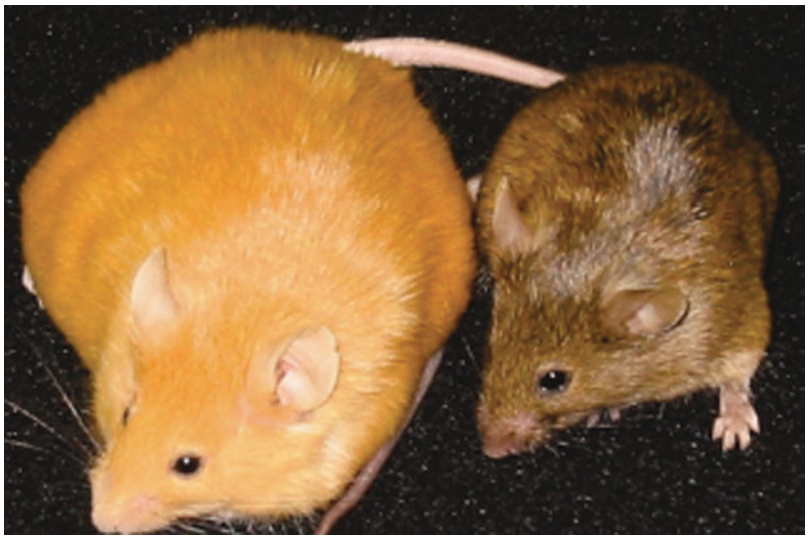


Figure 6.19 Methylation Counters Effects of a Mutant Gene.
Both mice have a mutation in the *agouti* gene, but the mother of the mouse on the right received supplements high in methyl groups; the resulting methylation reduced expression of the mutant gene.

Source: Courtesy of Randy L. Jirtle, Duke University Medical Center.

A Further Look:

Obesity Alters Your DNA

Obesity is considered a pandemic disease by many who study it; the percentage of individuals who are overweight continues to rise and with it a whole host of related diseases, such as type 2 diabetes, heart disease, high blood pressure, and cancer. And there is increasing evidence that our exposure to an excess of calories can affect gene expression as early as in the womb (Lopomo, Burgio & Migliore, 2016). But are these epigenetic changes to our DNA permanent?

When Simone Wahl and her colleagues (2017) analyzed the correlation between methylation changes and BMI, they found that the majority of the correlations were consequences of obesity rather than the cause. The epigenetic changes appeared to be the result of altered lipid and glucose metabolism, and some were linked to risk for type 2 diabetes. The causal interpretation is supported by earlier evidence that weight loss can remove these genetic changes. In formerly obese individuals who have maintained their weight loss, methylation patterns are similar to those of normal-weight individuals (Huang et al., 2015). Even when the weight loss is brought about by surgery that restricts nutrient intake or absorption, the epigenetic profiles become similar to those of lean individuals (Barres et al., 2013). So the steps one takes to lose weight not only shift the dial on the bathroom scale but correct health-threatening changes that weight gain has wrought on the epigenome.

Obesity and Reduced Metabolism

Accounts of dieting are all too often stories of failure; overweight people report slavishly following rigorous diets without appreciable weight loss, or they lose weight and then gain it back within a year's time. One factor in the failures may be dieters' misrepresentation of their efforts, whether intentional or not. One group of diet-resistant obese individuals underreported the amount of food they consumed by 47% and overreported their physical activity by 51% (Lichtman et al., 1992).

But another critical element that can make weight loss difficult is a person's rate of energy expenditure. In the average sedentary adult, about 75% of daily energy expenditure goes into resting or **basal metabolism**, the energy required to fuel the brain and other organs and to maintain body temperature; the remainder is spent about equally in the two remaining components of metabolism, physical activity and digestion of food (Bogardus et al., 1986).

Differences in basal metabolism may be a key element in explaining differences in weight. When 29 women who claimed they could not lose weight were isolated and monitored closely while they were restricted to a diet of 1,500 kilocalories (kcal; a measure of food's energy value, popularly called *calorie*), 19 did lose weight, but 10 did not (D. S. Miller & Parsonage, 1975). The 10 who failed to lose weight turned out to have a low basal metabolism rate (BMR). Heredity accounts for about 40% of people's differences in BMR (C. Bouchard, 1989). When identical twins were overfed 1,000 calories per day for 3 months, the differences in weight gain within pairs of twins were only one third as great as the differences across pairs (C. Bouchard et al., 1990). As a result, some medical professionals have called for labeling obese individuals with low BMR as suffering from a disorder called *metabolic syndrome*.

However, a person's metabolism can shift when gaining or losing weight. In an unusual *experimental* manipulation, researchers had both obese and never-obese individuals either lose weight or gain weight (Leibel, Rosenbaum, & Hirsch, 1995). Those who lost weight shifted to reduced levels of energy expenditure, and the ones who gained weight increased their energy expenditure. The energy expenditure changes were greater than the weight changes would require, suggesting that the individuals' bodies were *defending* their original weight, called a set point (see Keesey & Powley, 1986). Individuals also defend against weight gain by increasing their physical activity, mostly through casual walking, fidgeting, and spontaneous muscle contraction (F. R. Levine, Eberhardt, & Jensen, 1999). Among volunteers overfed 1,000 calories per day, those who increased their energy expenditure the least gained 10 times as much weight.

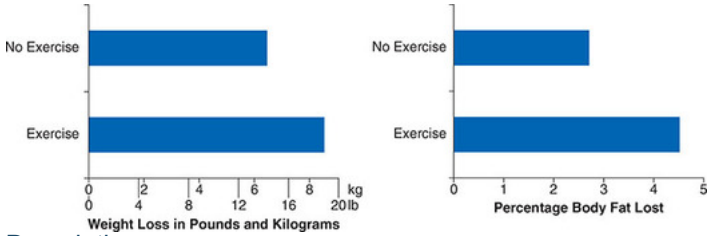
So why doesn't this defense of body weight prevent people from becoming obese? One reason is that the body defends less against weight gain than against weight loss (J. O. Hill et al., 2003). Humans evolved in an environment in which food was sometimes scarce, so it made sense for the body to store excess nutrients during times of plenty and to protect those reserves during famine. Such a system is adaptive when humans are at the mercy of nature, but it is a liability when modern agriculture and global transportation provide a constant supply of more food than we need.

Obese people tend to be more sedentary, sitting for longer periods of time—2 hours longer in one study (Levine et al., 2005). And unlike obesity-resistant individuals, those who are obesity-prone respond to overfeeding by decreasing the amount of time they spend walking (Schmidt, Harmon, Sharp, Kealey, & Bessesen, 2012) and by reducing their level of fat oxidation during the night (Schmidt, Kealey, Horton, VonKaenel, & Bessesen, 2013).

Prolonged weight gain may reset a person's set point at a higher level. Barbara Rolls and her colleagues (1980) fattened rats on highly palatable, high-energy junk food (chocolate chip cookies, potato chips, and cheese crackers) for 90 days. Surprisingly, when the rats were returned to their usual lab chow, they did not lose weight. The rats maintained their increased weight for the 4-month duration of the study—while eating the same amount of food as the control rats. They were defending a new set point. The researchers suggested that the variety of the foods offered, the length of the fattening period, and lack of exercise all contributed to the rats' failure to defend their original weight. In view of the difficulties in shedding excess weight, one obesity researcher pointed out that even modest weight loss reduces risk for chronic disease and suggested that a goal of 10% weight reduction is more practical than a return to normal weight (Pi-Sunyer, 2003).

Treating Obesity

There is no greater testimony to the difficulty of losing weight than the lengths to which patients and doctors have gone to bring about weight loss. These include wiring the jaws shut, surgically reducing the stomach's capacity, and removing fat tissue. The standard treatment for obesity, of course, is dietary restriction. However, we have seen that the body defends against weight loss, and dieters are usually frustrated. Besides burning fat, exercise during dieting may increase resting metabolic rate or at least prevent it from dropping (Calles-Escandón & Horton, 1992). Dieters who exercise lose more weight than dieters who do not exercise (Figure 6.20; J. O. Hill et al., 1989). In a study of formerly obese women, 90% of those who maintained their weight loss exercised, compared with 34% of those who regained their lost weight (Kayman, Bruvold, & Stern, 1990).



Description

Figure 6.20 The Effect of Exercise on Weight Loss.
Dieters who also exercised lost 32% more weight than those who did not, and they lost 40% more body fat.

Source: Based on data from J. O. Hill et al., 1989.

? How can obesity be treated effectively?

Another option in the treatment of obesity is medication. However, the history of this alternative has been fraught with problems, including minimal effectiveness and sometimes health-threatening side effects. After several drugs were withdrawn for safety reasons, by 2010, only orlistat remained available in the United States. Because orlistat blocks fat absorption, it often causes digestive discomfort and in some cases damage to the liver, kidneys, and pancreas; its discontinuation rate is 30% (Daneschvar, Aronson, & Smetana, 2016). The first new drugs in 13 years began arriving in 2012, until four additional medications had won approval; the paucity of drugs indicates the inherent difficulty in pharmacological treatment of obesity. The mechanisms of these new drugs are varied, ranging from enhancing serotonin transmission to antagonizing opioid receptors. They also have adverse side effects, but less so than their predecessors. Anti-obesity drugs are no panacea; they add only modest benefit beyond dieting and exercise alone, which, by the way, are still part of the regimen.

Serotonin plays an interesting role in weight control. Carbohydrate regulation involves a feedback loop; eating carbohydrates increases serotonin levels, which inhibits a person's appetite for carbohydrates (Leibowitz & Alexander, 1998), apparently by reducing NPY activity (Dryden, Wang, Frankish, Pickavance, & Williams, 1995). Drugs that block serotonin reuptake reduce carbohydrate intake, but only in the group of obese individuals who crave carbohydrates and eat a large proportion of their diet in carbohydrates (Lieberman, Wurtman, & Chew, 1986; Wurtman, Wurtman, Reynolds, Tsay, & Chew, 1987). Serotonin also enhances mood in some people (an important factor in some antidepressants), and people who have trouble maintaining weight loss often say that they use food to make themselves feel better when they are upset (Kayman et al., 1990). A high-carbohydrate meal also improves mood only in carbohydrate cravers; it actually lowers the mood of noncravers and makes them feel fatigued and sleepy (Lieberman et al., 1986). So serotonin dysregulation may be an important contributor to obesity in a subset of people.

By now you should be asking, "Why not try the body's own hormones as weight loss drugs?" And, of course, researchers have thought of that as well. Although gastric bypass patients who lost the most weight also showed elevated PYY levels

(Buchwald et al., 2009), attempts to use PYY by itself have so far been unsuccessful, because of either a lack of effect or a side effect of extreme nausea (De Silva & Bloom, 2012). Leptin is particularly attractive to obesity researchers because, unlike food restriction, it increases metabolism (N. Levin, Nelson, Gurney, Vandlen, & de Sauvage, 1996), and it targets fat reduction while sparing lean mass (P. Cohen & Friedman, 2004). Leptin was administered to three severely obese children who produced no leptin at all due to a mutation in the *ob* gene (Farooqi et al., 2002). Their body weights decreased throughout treatment, although they were increasing in age; more than 98% of the weight loss was in fat mass, while lean mass increased. Figure 6.21 shows how dramatic the effects were in one of the children. Unfortunately, leptin treatment benefits only the 5% to 10% of obese people who are leptin deficient; the rest are resistant to leptin's effects, apparently as a result of long-term high-fat consumption (Enriori et al., 2007; Maffei et al., 1995). Many obesity researchers now believe that leptin's main role is in protecting the individual against weight loss during times of deprivation rather than against weight gain during times of plenty (Marx, 2003).

Figure 6.21 A Leptin-Deficient Boy Before and After Treatment.
(a) At age 3.5 years when treatment began and (b) at age 8, at normal weight.

Source: Courtesy of Sadaf Farooqi and Stephen O'Rahilly.

A more recent therapeutic approach involves treating out-of-control eating as an addictive behavior. Compulsive overeating and drug addiction share several behavioral and neurophysiological similarities, including distress during abstinence or dieting, high relapse rate, self-medication in response to negative emotional states, dopamine release in response to cues, and reduced numbers of dopamine D_2 receptors (Figure 6.22), with associated decreases in metabolism in prefrontal areas involved in impulse control (Lerma-Cabrera, Carvajal, & Lopez-Legarrea, 2016; V. H. Taylor, Curtis, & Davis, 2009). In addition, signals that influence eating—orexin, insulin, leptin, and ghrelin—also increase or decrease activity in the reward system (Volkow, Wang, Tomasi, & Baler, 2013). Some drugs used in addiction treatment have shown promise for treating obesity. Contrave, one of the approved anti-obesity drugs, is a combination of naltrexone and bupropion, both of which are used to treat addiction (see Chapter 5).

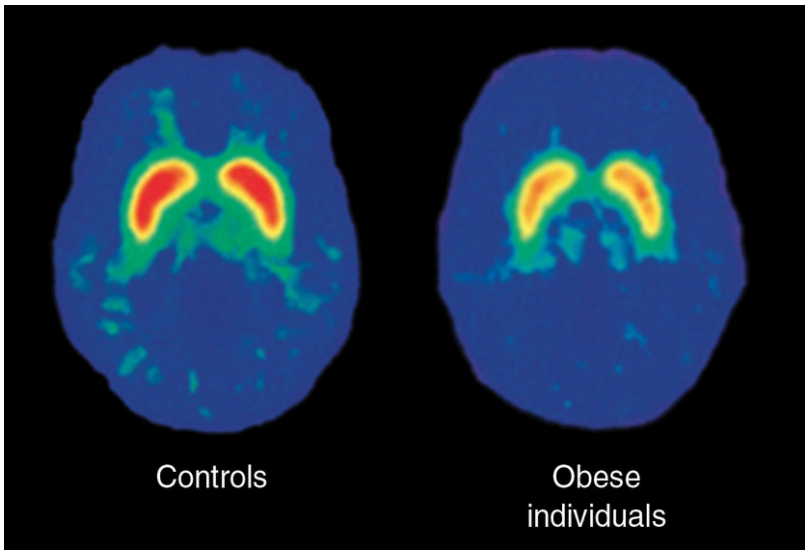
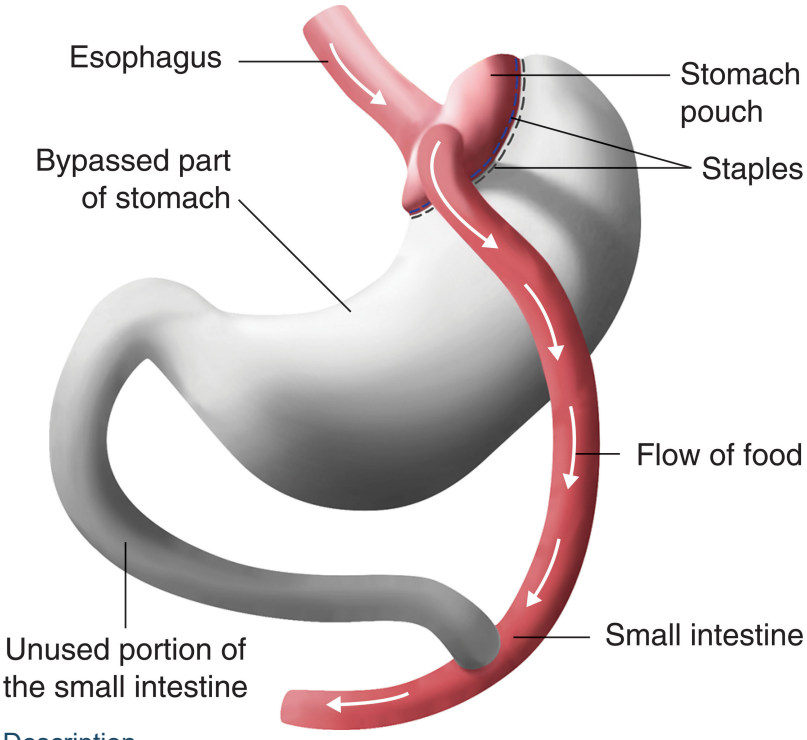


Figure 6.22 Diminished Number of Dopamine D_2 Receptors in Obese Individuals. Less intense colors in the PET scan of obese individuals (showing the group average) reveal that D_2 receptors are reduced in the same areas as in individuals with drug addictions.

Source: Reprinted from *The Lancet*, G.-J. Wang et al., "Brain Dopamine and Obesity," Lancet, 357, pp. 354-357, with permission from Elsevier.

Unfortunately, lifestyle modification and approved drug therapies reduce body weight by only 5% to 10% (Mitka, 2006), and most dieters regain their weight within a year (Bray, 1992). That much weight reduction can lead to significant health gains, but it is not enough for the morbidly obese (BMI over 40; see Figure 6.15), who are increasingly turning to bariatric surgery. Two types of surgery reduce food consumption, either by removing part of the stomach or by banding it to reduce its capacity. The most effective procedure, gastric bypass, reduces the stomach to a small pouch, which is then reconnected at a lower point on the intestine (Figure 6.23). This both limits meal size and reduces nutrient absorption in the digestive tract. Bariatric surgery costs between $14,500 and $23,000 in the United States, depending on the type of surgery ("Weight Loss Surgery Insurance Coverage and Costs," 2016), but the benefits can be remarkable. The resulting weight loss averages 32% after 1 or 2 years and is maintained at 25% 10 years later (Sjöström et al., 2007). The weight loss engenders a cascade of additional benefits: remission of type 2 diabetes in 77% of patients, hypertension in 66%, and sleep apnea in 88% (Buchwald et al., 2004), as well as a 27% reduction in mortality at 15 years (Sjöström et al., 2007). Reducing digestive capacity is not the only way bypass surgery brings about weight reduction: Blood glucose control improves (Rubino et al., 2016); postmeal ghrelin levels are decreased, and PYY is increased (Pournaras & le Roux, 2009), so the individual doesn't feel hungry; and even the balance of intestinal microbes improves (Kong et al., 2013). Surgery is a last resort, though, and its downsides further highlight the need for weight management and obesity prevention. A Further Look suggests a surprising way of protecting children from becoming overweight.



Description

Figure 6.23 Gastric Bypass Procedure.
A small area of the stomach is isolated from the rest. Then the small intestine is severed, and the cut end is attached to the pouch, reducing the length of the intestine and the amount of nutrient absorption.

Source: Adapted from Ainsworth (2009).

A Further Look:

Pets May Provide Protection Against Obesity

Many parents think a dog or cat can help their child learn responsibility or engage in more physical activity, but new research suggests that just exposure to pets, even while still in the womb, can be beneficial. Researchers at the University of Alberta Department of Pediatrics have been studying how prenatal and postnatal exposure to furry animals, such as cats and dogs, affects the types of bacteria found in the guts of infants (Tun et al., 2017). The messy work of analyzing fecal samples is rewarding researchers with evidence that the types of bacteria found in the gut are associated with risk for a variety of psychological and physical conditions. Infants with pet exposure had higher amounts of two “good” bacteria, *Oscillospira* and *Ruminococcus*, compared with infants without pet exposure. *Oscillospira* previously has been found in the guts of people with healthy BMIs, and *Ruminococcus* seems to protect against illness. With increasing rates of childhood obesity, the discovery that a household pet can promote helpful bacterial development in the guts of children suggests new possibilities in obesity and illness prevention.

Not everyone with an eating disorder is overweight or obese. Some people try so hard to control their weight that they eat less than is needed to maintain health, or they eat normal or excess amounts and then vomit or use laxatives to avoid gaining weight. As you will see, anorexia and bulimia are as puzzling to researchers as obesity and often more deadly for the victims.

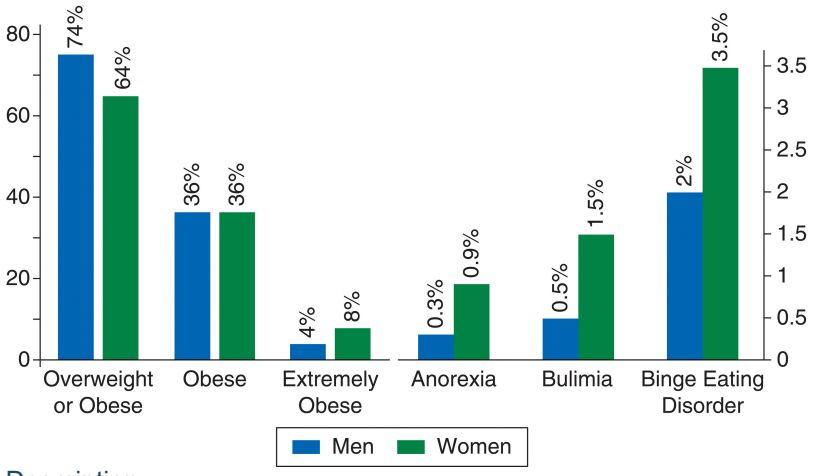
Concept Check

Take a Minute to Check Your Knowledge and Understanding

- What are the causes of obesity? Of the current surge in obesity?
- How does defense of body weight contribute to obesity?
- What are the problems in treating obesity?

ANOREXIA, BULIMIA, AND BINGE EATING DISORDER

Difficulties with eating and weight regulation affect women much more often than they do men. Though men are overrepresented among U.S. adults who are overweight or obese, women outnumber men two to one among the extremely obese (U.S. Department of Health and Human Services, 2012). Similarly, women are three times as likely to be diagnosed with anorexia nervosa or bulimia nervosa and twice as likely to suffer from binge eating disorder (Figure 6.24; Hudson, Hiripi, Pope, & Kessler, 2007). The reasons are not well understood, so they will not be addressed here, but we want you to understand why most of the studies described here involve women or girls.



Description

Figure 6.24 Prevalence by Sex of Overweight, Obesity, and Eating Disorders.

Source: Based on data from Hudson, Hiripi, Pope, and Kessler (2007); U.S. Department of Health and Human Services (2012).

Anorexia nervosa is known as the “starving disease” because the individual restricts food intake to maintain weight at a level so low that it is threatening to health (Figure 6.25; Walsh & Devlin, 1998). The person may also exercise for hours a day or resort to vomiting to control weight loss. People with anorexia often see themselves as fat even when they are emaciated. They are likely to deny the need for treatment and fail to comprehend the medical consequences of their disorder. There are two types of anorexia. *Restrictors* rely only on reducing food intake to control their weight. *Binge-purgers* restrict their calorie intake as well, but they also resort to vomiting or using laxatives. If anorexia continues long enough, it leads to cessation of ovulation, loss of muscle mass, heart damage, and reduction in bone density. The mortality rate is the highest of any psychiatric illness, more than double that for female psychiatric patients; half of the deaths are from complications of the disease and another quarter

from suicide (Sullivan, 1995). Still, most patients recover, though it can take years; in one study, about one third of women had recovered after 9 years and another third at the 22-year follow-up (Eddy et al., 2017).

Figure 6.25 French Model Isabelle Caro in Late Stages of Anorexia.
Caro, who suffered from anorexia from the age of 13, fell into a coma when her weight dropped to 55 pounds. That experience led her to pose for photos that appeared in newspapers and on billboards as part of an Italian anti-anorexia campaign. She died 3 years later at the age of 28; her mother committed suicide over the guilt she felt.

Source: Agencia el Universal/El Universal de Mexico/Newscom

? What are anorexia, bulimia, and binge eating disorder?

Numerous studies have found anomalies in brain structure and function in anorexia patients. Brain scans show deficits in gray matter extending over wide areas of the brain (Mainz, Schulte-Rüther, Fink, Herpertz-Dahlmann, & Konrad, 2012). These appear to be only partially reversible following weight recovery; in fact, this persistence is so reliable that studies of brain structure and function often focus on recovered individuals as a way of avoiding effects due to starvation. Brain scans also reveal dysfunction in areas involved in reward, emotion, behavioral control, and body image (W. H. Kaye, Fudge, & Paulus, 2009). Following 16 hours of fasting, healthy women showed activation of reward circuits during a monetary task; women in remission from anorexia were unresponsive to rewards, but they did activate cognitive behavioral control circuits (prefrontal cortex and insula), both when fasting and after eating (Wierenga et al., 2014). When choosing foods, newly hospitalized patients activated the dorsal striatum, an area involved in habitual behavior, more than did healthy controls (Foerde, Steinglass, Shohamy, & Walsh, 2015). These results are consistent with patients' control over hunger and eating behavior, a control that relies on automatic learned behaviors rather than an assessment of bodily needs. In recovered women with anorexia, connections are weakened between the anterior cingulate cortex and the rest of the brain (Reininghaus et al., 2016). This area is involved in impulse control, emotion, and decision making, so the disconnection makes it more difficult to recognize the danger posed by weight loss. Communication was also found to be impaired between two visual projection areas involved in body perception, and the weaker the connection, the more the women overestimated their body size (Suchan et al., 2013).

Bulimia nervosa also involves weight control, but the behavior is limited to bingeing and purging. If the bulimic restricts food intake, it is only for a few days at a time, and restricting takes a backseat to bingeing and purging. In fact, only 19% of bulimic women consume fewer calories than normal controls, whereas 44% overeat (Weltzin, Hsu, Pollice, & Kaye, 1991). Most women with bulimia are of normal weight (Walsh & Devlin, 1998), but there are indications that they might be battling hunger. Their ghrelin levels between meals are one third higher than in controls and decrease less following a meal; in addition, PYY levels do not rise as much following a meal (Kojima

et al., 2005). Bulimia carries a risk for heart problems and diabetes, and frequent purging damages the esophagus, gums, and teeth and leads to electrolyte depletion and dehydration. Like anorexia, bulimia is also difficult to treat; although three quarters of patients appear to be fully recovered after 8 years, one third of these relapse (D. B. Herzog et al., 1999).

People with **binge eating disorder** frequently eat large amounts of food during a short period of time, and they feel they cannot control what or how much they eat. Because the individuals do not attempt to control weight by fasting, purging, or exercising, they typically are overweight, but this is not a requirement for diagnosis. They usually feel disgust and shame about their overeating, so they often choose to eat separately from others and do their bingeing in seclusion. Binge eating disorder has been recognized clinically only during the last 40 years and was included as a disorder for the first time in the 2013 revision of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*-5; American Psychiatric Association, 2013).

In addition to these three disorders and obesity, there are other eating disorders recognized by the *DSM*-5. These include night eating disorder (excessive eating between sleep bouts), pica (compulsive eating of dirt, chalk, and other non-food objects), rumination disorder (bringing back up and rechewing or spitting out previously swallowed food), and avoidant/restrictive food intake disorder (lack of interest in or concern about eating). Clearly, all are maladaptive and potentially harmful to the individual suffering from these disorders.

Environmental and Genetic Contributions

Both anorexia and bulimia involve a preoccupation with weight and body shape. Because increases in anorexia and bulimia seem to have paralleled an increasing cultural emphasis on thinness and beauty, some researchers have concluded that the cause is social. The male–female difference is consistent with this argument, because women are under more pressure to be slim, while men are encouraged to "bulk up." Cases are more common in Western, industrialized countries, where an impractical level of thinness is promoted by actors, models, and advertisers. Anne Becker of Harvard Medical School has been studying eating habits in the Pacific islands of Fiji since 1988 (Becker, Burwell, Gilman, Herzog, & Hamburg, 2002). Traditionally, a robust, muscled body has been valued for both sexes there. But when satellite television arrived in 1995, the tall, slim actors in shows such as *Beverly Hills, 90210* became teenage Fiji's new role models. By 1998, 74% of young island girls considered themselves too big or fat, even though they were not more overweight than others. Young girls who lived in homes that owned a TV were three times more likely to have an eating problem. Among 17-year-old girls, 11% admitted they had vomited to control weight, compared with just 3% in 1995.

? What is the evidence for social and genetic influences in anorexia and bulimia?

There is little doubt that social pressure contributes to anorexia and bulimia. But the disorders are not unknown in non-Westernized societies, and anorexia has been reported for 300 years, long before the cultural emphasis on thinness. One indication that a sociocultural explanation is an oversimplification is that several studies show a genetic influence. Relatives of patients have a higher than usual incidence of the disorders, and the concordances for anorexia and bulimia are about three times greater for identical twins than for fraternals (Kendler et al., 1991; Kipman, Gorwood, Mouren-Simeoni, & Ad'es, 1999). Heritability has been estimated at 56% for anorexia (Bulik, et al., 2006), 54% to 83% for bulimia (Thornton, Mazzeo, & Bulik, 2011), and 45% for binge eating disorder (K. S. Mitchell et al., 2010).

There has been no shortage of candidate genes, but definitive results have been elusive; this is due to a variety of reasons, including the apparent involvement of many small-effect genes, difficulty acquiring adequate numbers of patient volunteers, and the failure of studies to distinguish between the two subtypes of anorexia. A large study of 17,000 cases of anorexia found eight genetic locations correlated with anorexia as well as with psychiatric disorders, heightened physical activity, metabolic traits, and body measurements (H. J. Watson et al., 2019). Other results have

implicated a serotonin receptor gene and a dopamine receptor gene in anorexia, estrogen and cannabinoid genes that influence food intake in bulimia, and a serotonin transporter gene in binge eating disorder (Trace, Baker, Peñas-Lledó, & Bulik, 2013).

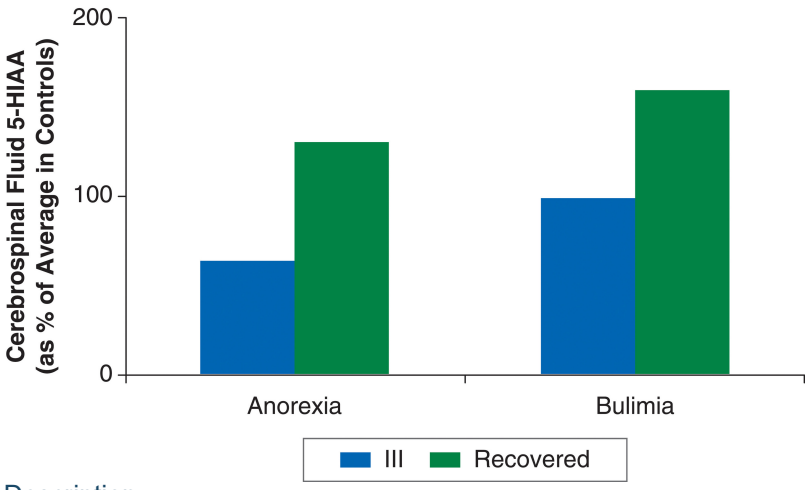
When researchers followed 772 female twins through adolescence, they made a surprising discovery (Klump, Burt, McGue, & Iacono, 2007). At age 11, genetic factors accounted for just 6% of disordered eating symptoms, such as weight preoccupation, body dissatisfaction, and binge eating, but by age 14, they accounted for 46% of the variance. Almost all the nongenetic influence is unique to the individual (Bulik et al., 2006; Bulik, Sullivan, Wade, & Kendler, 2000; K. S. Mitchell et al., 2010), which suggests the possibility that adolescent hormonal changes, stress, and dieting (and, possibly, prenatal conditions) produce epigenetic changes in the genes that play a role in anorexia and bulimia. There has been relatively little research in this area, but epigenetic dysregulation of dopamine genes has been reported in women with anorexia and bulimia (Frieling et al., 2010).

Eating disorders typically are accompanied by comorbid psychological disorders; in a study of 2,436 female inpatients, almost all were diagnosed with depression, more than half had anxiety disorders, 22% had substance abuse disorders, and the rates of obsessive-compulsive disorder varied from 15% to 29% across the groups (Blinder, Cumella, & Sanathara, 2006). Studies have also confirmed genetic associations of eating disorders with depression and obsessive-compulsive disorder (Scherag, Hebebrand, & Hinney, 2009). Because you know the limitations of correlational studies, you should be thinking that there are three possible reasons for this relationship: The psychological disorders could trigger disordered eating, starvation or overeating could precipitate an emotional disorder, or both of these could be the result of a third underlying cause. For us, the immediate value is that the characteristics of these comorbidities lead us to look at the transmitters involved in the emotional disorders and in reward and substance abuse.

The Role of Neurotransmitters

? What role does serotonin appear to have in anorexia and bulimia?

Researchers have focused most on serotonin, largely because it is involved so intimately in eating behavior and in mood disorders such as anxiety, depression, obsessiveness, and impulsive behavior that typically accompany the eating disorders (W. Kaye, Gendall, & Strober, 1998). Because antidepressants that increase serotonin availability reduce the bingeing and purging of bulimia and lower the chance of relapse after recovery from anorexia, researchers looked for evidence of decreased serotonin activity. However, levels of serotonin metabolites were normal in patients with bulimia, and they were low in those with anorexia only during illness, when their starvation diet provided too little tryptophan, the precursor to serotonin. After weight recovery, levels were higher than normal in both groups (Figure 6.26). This suggests that both groups produce excess serotonin in response to food. High serotonin levels are associated with anxiety and harm avoidance, which involves fearfulness in the face of uncertainty; starving or purging apparently is a strategy to avoid these consequences of high serotonin (W. Kaye et al., 1998; W. H. Kaye et al., 2009). Binge eating disorder does appear to involve chronically low serotonin levels, with binge eating serving to increase serotonin and alleviate depression (Haedt-Matt & Keel, 2011). However, bingeing is alleviated by antidepressants that do not increase serotonin levels, suggesting that additional neurotransmitters are involved (Berkman et al., 2015).



Description

Figure 6.26 Cerebrospinal Fluid 5-HIAA in Anorexia and Bulimia.
Values are compared with levels in healthy control women, which are set at 100%. 5-HIAA (5-hydroxyindoleacetic acid) is a metabolite of serotonin, and the level found in cerebrospinal fluid is used to estimate serotonin activity.

Source: Adapted from "Serotonin Neuronal Function and Selective Serotonin Reuptake Inhibiitor Treatment in Anorexia and Bulimia Nervosa," W. Kaye, K. Gendall, & M. Strober, *Biological Psychiatry*, 44, 825-838. Copyright, 1998. Used with permission from Elsevier.

According to Ursula Bailer and Walter Kaye (2010), another important factor is an imbalance in the number of 1A and 2A serotonin receptors. Imaging studies have found increased transmitter binding at 1A receptors and diminished binding at 2A receptors in anorexia and bulimia patients. This ratio imbalance is known to play a role in anxiety, depression, compulsive behavior, and harm avoidance; Bailer and Kaye point to evidence that experimentally depleting tryptophan reduces anxiety in both ill and recovered individuals and suggest that food restriction serves to reduce anxiety by depriving $5HT_{1A}$ receptors of serotonin.

A second neurotransmitter that figures prominently in eating disorder research is dopamine. Dopamine metabolites are reduced in the cerebrospinal fluid of individuals with anorexia, both during illness and after recovery (W. H. Kaye, Frank, & McConaha, 1999). Increasing dopamine activity by administering amphetamine produces euphoria in most people, but in women recovered from anorexia, it increases anxiety (Bailer et al., 2012). Because eating increases dopamine release, this finding lends additional support to the idea that food restriction serves to reduce anxiety. In women recovered from anorexia and bulimia, dopamine binding was correlated with harm avoidance; serotonin binding was associated with harm avoidance only in combination with dopamine binding, suggesting that serotonin has a modulating role on dopamine activity (Bailer et al., 2013). Increased binding to dopamine receptors in the dorsal striatum, possibly as a response to decreased dopamine levels, is associated with higher levels of harm avoidance in weight-recovered anorexia patients (Frank et al., 2005). Binge eating disorder is less researched than anorexia and bulimia, but it appears to be caused by increased pleasure from food and impaired decision making, both related to alterations in dopamine pathways characteristic of other impulsive and compulsive disorders such as substance abuse (R. M. Kessler, Hutson, Herman, & Potenza, 2016).

Anorexia patients' distinctive lack of enjoyment and ability to deny themselves not only food but other pleasures of life suggest that disordered reward systems might also be at work (Cassin & von Ranson, 2005). The reward system is far from unresponsive. In most neurons in the reward system, firing rate signals prediction error rather than reward, remaining at baseline in response to expected rewards, increasing when a reward is greater than expected, and decreasing when the reward is less than expected (Schultz, 2016). Adolescent girls who were recovered from

anorexia gave exaggerated prediction error responses in a taste-conditioning task when the sweet reward stimulus was omitted (Frank et al., 2018). So why were they so unresponsive to food when they were ill? The girls in the control group had strong functional connections between the hypothalamus and the ventral striatum, which includes the nucleus accumbens and is an important pathway in feeding regulation. But in this study and in an earlier one with both anorexic and bulimic women (Frank, Shott, Riederer, & Pryor, 2016), the individuals with eating disorders had strong connections from the ventral striatum to the hypothalamus, a pathway that mediates fear. Presumably this pathway overrides hunger signals from the hypothalamus.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- What are the likely causes of anorexia and bulimia?
- How are anorexia and bulimia alike and different? (Don't forget the two types of anorexia.)

IN PERSPECTIVE

Temperature regulation, thirst, and hunger provide good examples of drive, homeostasis, and physiological motivation in general. Although they are explained best by drive theory, they also illustrate the point that it is ultimately the balance or imbalance in certain brain centers that determines motivated behaviors.

In addition, hunger in particular demonstrates that homeostasis alone does not explain all the facets of motivated behavior. For instance, we saw that the incentives of the sight and smell of food are enough to start the physiological processes involved in the absorptive phase. This suggests that incentives operate through physiological mechanisms and are themselves physiological in nature. We also know that there are important social influences on what and how much people eat, and sensation seeking may explain why some people are gourmets or enjoy the risks of eating puffer fish.

Most of the factors that determine our eating behavior are in turn influenced by genes. If it is true that we are what we eat, it is equally true that what we eat (and how much) is the result of who we are. But we will be reminded time and again throughout this text that heredity is not destiny, that we are the products of countless interactions between our genetic propensities and the environment.

Our interest in the motivation of hunger would be mostly theoretical if it were not for eating disorders, which can have life-threatening consequences. Despite their importance, we are unsure about the causes of obesity, anorexia, bulimia, and binge eating disorder, as well as what the best treatments are. We do know that, like the motivation of hunger itself, these disorders are complex and have a number of causes.

This chapter has given you an overview of what we mean by motivation. We will broaden that view in the next two chapters by looking at sexuality, emotion, and aggression.

Chapter Summary

Motivation and Homeostasis

- Homeostasis and drive theory are key to understanding physiological motivation, but they are not adequate alone.
- Temperature regulation involves a simple mechanism for control around a set point.
- Thirst is a bit more complex, compensating for deficits both in the cells (osmotic thirst) and outside the cells (hypovolemic thirst).

Hunger: A Complex Drive

- Hunger is a more complex motivation, involving a variety of nutrients and regulation of both short-term and long-term nutrient supplies.
- Taste helps an individual select nutritious foods, avoid dangerous ones, and vary the diet.
- The feeding cycle consists of an absorptive phase, a period of living off nutrients from the last meal, and the fasting phase, when reliance shifts to stored nutrients.
- Eating is initiated when ghrelin is high and glucose and fatty acids are low. The information is sent to the medulla and to the paraventricular nucleus of the hypothalamus, where neuropeptide Y is released to initiate eating.
- Feeding stops when stretch signals from the stomach, increasing glucose levels in the liver, and cholecystokinin released in the duodenum indicate that satiety has occurred.
- How much we eat at a meal is also regulated by the amount of fat we have stored, indicated by leptin and insulin levels.

Obesity

- Obesity is associated with malnutrition and with a variety of illnesses.
- A variety of factors, many of them outside the person’s control, contribute to obesity.
- Obesity is partly inheritable, and the environmental influences that exist are not primarily from the family.
- As calorie intake decreases, metabolism decreases to defend against weight loss.
- Obesity is difficult to treat, but drugs that increase serotonin activity appear most promising, and bariatric surgery is beneficial for more extreme obesity.

Anorexia, Bulimia, and Binge Eating Disorder

- Anorexia involves restriction of food intake, and sometimes bingeing and purging, to reduce weight. Bulimia is a bingeing disease; weight increase is limited by purging or exercise. People with binge eating disorder eat excessively during a brief period of time; they are typically, but not always, overweight.
- Both social pressure and heredity appear to be important in anorexia and bulimia.
- Family and twin studies indicate a strong hereditary component, though few genes have been reliably identified. The large amount of individually unique environmental influence suggests epigenetic effects.
- Anomalies in serotonin, dopamine, and reward systems also are implicated.

Study Resources

For Further Thought

- If a group of nuclei in the brain control a particular homeostatic need, what functions must those nuclei carry out?
- What do you think would happen if the brain had no way of monitoring stored fat levels?
- Several of the controls of eating seem to duplicate themselves. Is this wasteful or useful? Explain.
- What do you think a complete program of obesity treatment would look like?
- Describe a comprehensive experimental treatment program for anorexia, bulimia, or binge eating disorder.

Test Your Understanding

1. Describe either temperature regulation or thirst in terms of homeostasis, drive, and satisfaction, including the signals and brain structures involved in the process.
2. Describe the absorptive and fasting phases of the feeding cycle; be specific about what nutrients are available, how nutrients are stored, and how they are retrieved from storage.
3. Describe obesity as a problem of metabolism.

Select the best answer:

1. A problem that makes some people question the adequacy drive theory is that
    1. an animal remains aroused after the need is satisfied.
    2. some people have stronger drives than others.
    3. not all motivation involves tissue needs.
    4. soon after a drive is satisfied, the system goes out of equilibrium again.
2. An animal is said to be in homeostasis when it
    1. recognizes that it is satisfied.
    2. feels a surge of pleasure from taking a drink.
    3. is in the middle of a high-calorie meal.
    4. is at its set-point temperature.
3. Osmotic thirst is due to

    1. dryness of the mouth and throat.
    2. lack of fluid in the cells.
    3. reduced volume of the blood.
    4. stimulation of pressure receptors.
4. A structure in the medulla that is involved in taste as well as in hunger and eating is the
    1. nucleus of the solitary tract.
    2. paraventricular nucleus.
    3. area postrema.
    4. subfornical organ.
5. The research that controlled sheep predation suggests that you might keep rabbits from eating your garden by
    1. spraying the plants daily with a substance that tastes too bad to eat.
    2. spraying the plants occasionally with a substance that makes the rabbits sick.
    3. spraying the plants with a poison until all the rabbits are gone.
    4. running outside and chasing the rabbits away.
6. During the absorptive phase,
    1. fat is broken down into glycerol and fatty acids.
    2. insulin levels are low.
    3. glucagon converts glycogen to glucose.
    4. glucose from the stomach is the main energy source.
7. Neurons in the arcuate nucleus release NPY, which
    1. increases eating.
    2. increases drinking.
    3. breaks down fat.
    4. causes shivering.
8. A long-term signal that influences eating is
    1. glucose.
    2. 2-deoxyglucose.
    3. cholecystokinin.
    4. leptin.
9. Regarding environmental influences on weight,
    1. smoking increases appetite.
    2. the influence of infection has been disproven.
    3. sleep loss increases appetite.
    4. social influence is mostly from the family.
10. When we say that the body defends weight during dieting, we mean primarily that
    1. the person's metabolism decreases.
    2. the person eats less but selects richer foods.
    3. the person eats lower-calorie foods but eats larger servings.
    4. the body releases less NPY.
11. Studies comparing the weights of adopted children with their biological parents and their adoptive parents
    1. show that weight is influenced most by environment.
    2. show that weight is influenced most by heredity.
    3. show that heredity and environment have about equal influence.
    4. have not been in agreement.
12. If a *db/db* mouse is parabiotically attached to a normal mouse, the *db/db* mouse will
    1. gain weight while the normal loses.
    2. lose weight while the normal gains.
    3. be unaffected while the normal loses.
    4. be unaffected while the normal gains.
13. Epigenetic effects on offspring weight have resulted from the mother's
    1. drug use.
    2. activity level.
    3. diet.
    4. smoking.
14. Which of the following was not discussed as a factor in anorexia and/or bulimia?
    1. Increased numbers of nicotinic acetylcholine receptors.
    2. An imbalance in types of serotonin receptors.
    3. Reduced dopamine activity.

    4. Stronger connections with the ventral striatum.
15. Regarding anorexia and bulimia,
    1. both are characterized by a deficiency in hunger.
    2. evidence indicates that epigenetic changes occur during adolescence.
    3. they appear to be uniquely distinct from other disorders.
    4. antidepressants help with anorexia but not bulimia.

Answers:

1. c, 2. d, 3. b, 4. a, 5. b, 6. d, 7. a, 8. d, 9. c, 10. a, 11. b, 12. c, 13. c, 14. a, 15. b.

For Further Reading

1. In “Overfat and Underfat: New Terms and Definitions Long Overdue,” Phillip Maffetone, Ivan Rivera-Dominguez, and Paul Laursen (*Frontiers in Public Health*, January 3, 2017) argue that 76% of the world’s population is “overfat.” This includes not only the obese and overweight but also people who are normal in weight but carry extra fat, particularly around the belly, increasing their risk for chronic and metabolic disease.
2. Researchers are continuing to discover maternal epigenetic influences on offspring risk of obesity, including stress (*Obesity Research*, 2015, *16*, 351–361), high-fat diet (*Diabetes*, 2016, *65*, 574–584), and poor sleep (*Diabetes*, 2014, *63*, 3230–3241).
3. There is no shortage of hypotheses about what causes anorexia, but if one possible cause is confirmed, it could lead to an additional treatment option. Researchers at the French National Institute of Health and Medical Research have found that antibodies to a protein produced by normal intestinal bacteria are elevated in anorexia patients and that the antibodies also attack the satiety hormone melanotropin (*Translational Psychiatry*, 2014, *4*, e458).
4. “Full Without Food,” by Claire Ainsworth (*New Scientist*, September 5, 2009, 30–33), describes surgery for obesity and emphasizes its benefits for diabetics, as well as the possibility of creating drugs that mimic the effects of GLP-1, which is increased following the surgery.
5. “The Archaeology of Food,” by Katheryn Twiss (Cambridge University Press, 2019), is a fascinating exploration of ancient food traditions, with a strong focus on Middle Eastern food traditions in Turkey and Mesopotamia. In this book, she discusses religious practices, gender and ethnic norms, and how food and culture interact.

Key Terms

absorptive phase 172

amino acids 171

angiotensin II 165

anorexia nervosa 190

arcuate nucleus (ARC) 173

area postrema 171

arousal theory 163

basal metabolism 186

binge eating disorder 191

body mass index (BMI) 179

bulimia nervosa 191

cholecystokinin (CCK) 176

diabetes 172

diabetes gene 183

drive 163

drive theory 163

duodenum 171

epigenetic 184

fasting phase 172

fatty acids 171

ghrelin 175

glucagon 173

glucose 171

glycerol 171

glycogen 172

homeostasis 163

hypovolemic thirst 165

incentive theory 163

instinct 162

insulin 172

lateral hypothalamus (LH) 173

learned taste aversion 169

learned taste preference 170

leptin 177

median preoptic nucleus (MnPO) 165

motivation 162

neuropeptide Y (NPY) 173

NPY/AgRP neurons 173

obesity gene 183

orexin 174

organum vasculosum lamina terminalis (OVLT) 165

osmotic thirst 165

paraventricular nucleus (PVN) 174

peptide YY3–36 (PYY) 176

preoptic area 165

proopiomelanocortin (POMC) neurons 173

satiety 166

sensory-specific satiety 169

set point 163

subfornical organ (SFO) 165

ventromedial hypothalamus (VMH) 174

Descriptions of Images and Figures

Back to Figure

The sagittal view of the brain shows the hypothalamus. A magnified view shows the optic chiasm and the pituitary gland posterior to the hypothalamus. The nuclei of the hypothalamus are as follows:

- Anterior hypothalamus
- Preoptic area
- Suprachiasmatic nucleus
- Paraventricular nucleus
- Ventromedial hypothalamus
- Lateral hypothalamus
- Arcuate nucleus

Back to Figure

A magnified view of the sagittal brain shows the thalamus, hypothalamus, and the brain stem. Signals from the heart through cranial nerves pass through the nucleus of the solitary tract in the brain stem and reach the subfornical organ in the thalamus and organum vasculosum lamina terminalis in the hypothalamus. Signals from these two organs reach the median preoptic nucleus in the hypothalamus. Angiotensin 2 from the kidneys passes through the blood vessels and reaches subfornical organ in the thalamus and organum vasculosum lamina terminalis in the hypothalamus.

Back to Figure

The esophagus, extending from the mouth, leads to the following organs: Stomach, duodenum, small intestine, large intestine, rectum, and anal canal. The liver, gallbladder, and pancreas are the associated organs located close to the stomach.

Back to Figure

The stages in the absorptive phase are as follows:

- Glucose increases.

- Parasympathetic activation.
- Pancreas secretes insulin.
- Glucose enters body cells. Glucose stored in liver and muscles as glycogen. Fat stored in adipose cells as triglycerides.

The stages in the fasting phase are as follows:

- Glucose decreases.
- Sympathetic activation.
- Pancreas secretes glucagon.
- Glycogen transformed to glucose for brain. Stored fat released as fatty acids for body and glycerol for brain, after conversion to glucose.

Back to Figure

The illustration shows the sagittal view of the brain with a magnified view of the hypothalamus showing four nuclei: Paraventricular nucleus, lateral hypothalamus, arcuate nucleus, and ventromedial hypothalamus. Glucose, fatty acids, ghrelin from the stomach, insulin from the pancreas, leptin from the fat cells, and Peptide Y Y3-36 from the large intestine travel through the blood vessels and reach the hypothalamus. Glucose and fatty acids from the liver and small intestine, stomach volume from the stomach, and cholecystokinin from the duodenum travel through the vagus nerve and reach the hypothalamus. Glucose, fatty acids, and ghrelin cause initiation of eating. Glucose, fatty acids, insulin, leptin, Peptide Y Y3-36, stomach volume, and cholecystokinin cause inhibition of eating.

Back to Figure

The horizontal axis is labeled time of day, and ranges from 6 a.m. to 5 a.m. in hourly increments. The vertical axis is labeled ghrelin in picograms per milliliters, and ranges from 400 to 1,400 in increments of 100. The approximate data from the graph are tabulated below.

Back to Figure

In both graphs, the horizontal axis lists the preloaded solutions, and the vertical axis is labeled food consumed in milliliters, ranging from 0 to 8, in increments of 2. Graph a shows data for pylorus closed and graph b shows data for pylorus open. The approximate data from both graphs are tabulated below.

Back to Figure

The horizontal axis lists the individuals. The vertical axis is labeled Number in millions, and ranges from 0 to 400 in increments of 50. The approximate data from the graph are tabulated below.

Back to Figure

The chart lists height from 60 inches to 76 inches, with B M I calculated when weight is between 100 pounds and 260 pounds. The data from the chart, presented in the format, height in inches: 100 pounds, 105 pounds, 110 pounds, 115 pounds, 120 pounds, 125 pounds, 130 pounds, 135 pounds, 140 pounds, 145 pounds, 150 pounds, 155 pounds, 160 pounds, 165 pounds, 170 pounds, 175 pounds, 180 pounds, 185 pounds, 190 pounds, 195 pounds, 200 pounds, 205 pounds, 210 pounds, 215 pounds, 220 pounds, 225 pounds, 230 pounds, 235 pounds, 240 pounds, 245 pounds, 250 pounds, 255 pounds, 260 pounds, are as follows. 60: 20, 21, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 50. 61: 19, 20, 21, 22, 23, 24, 25, 26, 27, 27, 28,

29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 43, 44, 45, 46, 47, 48, 49. 62: 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48. 63: 18, 19, 19, 20, 21, 22, 23, 24, 25, 26, 27, 27, 28, 29, 30, 31, 32, 33, 34, 35, 35, 36, 37, 37, 38, 39, 40, 41, 42, 43, 43, 44, 45, 46. 64: 17, 18, 19, 20, 21, 21, 22, 23, 24, 25, 26, 27, 27, 28, 29, 30, 31, 32, 33, 33, 34, 35, 36, 37, 38, 39, 39, 40, 41, 42, 43, 44, 45.65: 17, 17, 18, 19, 20, 21, 22, 22, 23, 24, 25, 26, 27, 27, 28, 29, 30, 31, 32, 32, 33, 34, 35, 36, 37, 37, 38, 39, 40, 41, 42, 42, 43. 66: 16, 17, 18, 19, 19, 20, 21, 22, 23, 23, 24, 25, 26, 27, 27, 28, 29, 30, 31, 31, 32, 33, 34, 35, 36, 36, 37, 38, 39, 40, 40, 41, 42. 67: 16, 16, 17, 18, 19, 20, 20, 21, 22, 23, 23, 24, 25, 26, 27, 27, 28, 29, 30, 31, 31, 32, 33, 34, 34, 35, 36, 37, 38, 38, 39, 40, 41. 68: 15, 16, 17, 17, 18, 19, 20, 21, 21, 22, 23, 24, 24, 25, 26, 27, 27, 28, 29, 30, 30, 31, 32, 33, 33, 34, 35, 36, 36, 37, 38, 39, 40. 69: 15, 16, 16, 17, 18, 18, 19, 20, 21, 21, 22, 23, 24, 24, 25, 26, 27, 27, 28, 29, 30, 30, 31, 32, 32, 33, 34, 35, 35, 36, 37, 38, 38. 70: 14, 15, 16, 16, 17, 18, 19, 19, 20, 21, 22, 22, 24, 24, 24, 25, 26, 27, 27, 28, 29, 29, 30, 31, 32, 32, 33, 34, 34, 35, 36, 37, 37. 71: 14, 15, 15, 16, 17, 17, 18, 19, 20, 20, 21, 22, 22, 23, 24, 24, 25, 26, 26, 27, 28, 29, 29, 30, 31, 31, 32, 33, 33, 34, 35, 36, 36. 72: 14, 14, 15, 16, 16, 17, 18, 18, 19, 20, 20, 21, 22, 22, 23, 24, 24, 25, 26, 26, 27, 28, 28, 29, 30, 31, 31, 32, 33, 33, 34, 35, 35. 73: 13, 14, 15, 15, 16, 16, 17, 18, 18, 19, 20, 20, 21, 22, 22, 23, 24, 24, 25, 26, 26, 27, 28, 28, 29, 30, 30, 31, 32, 32, 33, 34, 34. 74: 13, 13, 14, 15, 15, 16, 17, 17, 18, 19, 19, 20, 21, 21, 22, 22, 23, 24, 24, 25, 26, 26, 27, 28, 28, 29, 30, 30, 31, 31, 32, 33, 33. 75: 12, 13, 14, 14, 15, 16, 16, 17, 17, 18, 19, 19, 20, 21, 21, 22, 22, 23, 24, 24, 25, 26, 26, 27, 27, 28, 29, 29, 30, 31, 31, 32, 32. 76: 12, 13, 13, 14, 15, 15, 16, 16, 17, 18, 18, 19, 19, 20, 21, 21, 22, 23, 23, 24, 24, 25, 26, 26, 27, 27, 28, 29, 29, 30, 30, 31, 32. The B M I values that are 18 and below are in blue, the values between 19 and 24 are in green, the values between 25 and 29 are in yellow, the values between 30 and 39 are in red, and the values that are 40 and above are in black.
Back to Figure

The horizontal axis ranges from 0 to 0.8 in increments of 0.2. The vertical axis lists three types of twins. The approximate data from the graph are tabulated below.

Back to Figure

The first pairing consists of an obese mouse with d b/d b gene and a normal-sized mouse with normal gene. Strong leptin signal is sent by the obese mouse to the normal mouse. The obese mouse is insensitive to the weak leptin signal received from the normal mouse. Text reads, Normal starves due to signal from d b/d b; d b/d b insensitive to Normal's signal.

The second pairing consists of an obese mouse with d b/d b gene and a normal-sized mouse with o b/o b gene. Strong leptin signal is sent by the obese mouse to the normal-sized mouse. Text reads, o b/o b starves due to signal from d b/d b.

The third pairing consists of an obese mouse with o b/o b gene and an overweight mouse with normal gene. Weak leptin signal is sent by the overweight mouse to the obese mouse. The overweight mouse is insensitive to the strong leptin signal received from the obese mouse. Text reads, Normal unaffected, but its signal slows o b/o b's weight gain.

Back to Figure

In the first graph, the horizontal axis is labeled weight loss in pounds and kilograms, and ranges from 0 to 8 kilograms in increments of 2 and 0 to 20 pounds in increments of 4. In the second graph, the horizontal axis lists percentage of body fat lost, and ranges from 0 to 5 in increments of 1. The approximate data from both graphs are tabulated below.

Back to Figure

The gastric bypass procedure involves stapling of the opening of the esophagus into the stomach pouch. The esophagus is bypassed through the stomach to the small

intestine, such that the flow of food from the esophagus is directly into the small intestine. A portion of the small intestine remains unused.
Back to Figure

The horizontal axis lists the conditions. The vertical axis ranges from 0 to 80 in increments of 10 for determining the prevalence of obesity. The vertical axis also ranges from 0 to 3.5 in increments of 0.5 for determining the prevalence of eating disorders. The data from the graph are tabulated below.

Back to Figure

The horizontal axis lists anorexia and bulimia. The vertical axis is labeled cerebrospinal fluid 5-H I A A as percent of average in controls, and ranges from 0 to 200 in increments of 100. The approximate data from the graph are tabulated below.

7 THE BIOLOGY OF SEX AND GENDER

Paul Gilham/Getty Images

Sex as a Form of Motivation

- Arousal and Satiation
- Hormonal Control of Sexual Behavior
- Brain Structures and Neurotransmitters
- Odors, Pheromones, and Sexual Attraction

A Further Look | Of Love, Bonding, and Empathy

Concept Check

The Biological Determination of Sex

- Chromosomes and Hormones
- Prenatal Hormone Influences on Brain and Behavior

Concept Check

Gender-Related Behavioral and Cognitive Differences

- Some Demonstrated Male–Female Differences
- Origins of Male–Female Differences

A Further Look | GTEx Project Provides New Insight Into the Differences Between the Sexes

Concept Check

Biological Origins of Gender Identity

- Transgender
- Transgender and the Brain
- 46,XY Intersex
- 46,XX Intersex

A Further Look | Sex, Gender, and Sports

- Cognitive and Behavioral Effects
- Ablatio Penis and Other Natural Experiments

A Further Look | Who Gets to Choose a Child's Sex?

Concept Check

Sexual Orientation

- The Social Influence Hypothesis
- Genetic and Epigenetic Influences
- Prenatal Influences on Brain Structure and Function
- Social Implications of the Biological Model

Concept Check

In Perspective

Chapter Summary

Study Resources

After reading this chapter, you will be able to

7.1 Contrast sex with other motivated behaviors.

7.2 Demonstrate the role of hormones, brain structures, and odors in sexual behavior.

7.3 Understand how chromosomes and hormones shape our development.

7.4 Identify hormonal and brain differences between females and males.

7.5 Determine the origins of male and female differences in behavior and cognition.

7.6 Explain the role of biological influences on gender identity.

7.7 Examine transgenderism, intersex, and their effects on the brain and behavior.

7.8 Assess the impact of biological influences on sexual orientation.

7.9 Describe the genetic, prenatal, and social influences on the biological model of sexual orientation.

Bruce Jenner spent his early career as an athlete, playing football at Graceland College until a knee injury necessitated a change in sport to decathlon in 1968. After years of grueling training and competition, Jenner won a gold medal in decathlon at the 1976 Summer Olympics in Montreal and became a hero back home in the United States. Jenner even graced the cover of *Sports Illustrated* magazine and became the most widely known athlete to be on the cover of a Wheaties breakfast cereal box. Leaving athletics behind, he became better known as a sports commentator and occasional actor in films and television. During this time, he had been married three times and fathered six children. Throughout his successes in athletics and as an actor, Jenner was struggling with a psychological disorder called gender dysphoria, which is the distress that people feel when their gender identity does not match their sex at birth. At times, he dressed as a woman, and he was taking female hormones to try to better match his feelings of being female.

In April 2015, Jenner made news by coming out as a transgendered woman. Later that year, Jenner officially adopted her now-permanent feminine identity as Caitlyn Jenner, and in January 2017, she underwent gender reassignment surgery to replace the penis with a vaginal opening. Her memoir *The Secrets of My Life* and the documentary series *I Am Cait* detailed her gender transition; in recognition of her outspoken support for LGBT rights and the strength she demonstrated in discussing her gender identity struggles with the public, she received the 2015 Arthur Ashe Courage Award and *Out* magazine's Newsmaker of the Year award. Quite possibly the most interesting thing about Caitlyn Jenner's new gender and identity is that she still finds herself sexually attracted to women, underscoring the fact that gender identity does not always match a person's sexual orientation.

Valerie Macon/AFP/Getty Images

Humans have a great affinity for dichotomies, dividing the world into blacks and whites, with few grays in between. No dichotomy is more significant for human existence than that of male and female: One's sex is often the basis for deciding how the person should behave, what the person can do, and with whom the person should fall in love. Not only are many of the differences between males and females imposed on them by society; Caitlyn's experience suggests that typing people as male or female may not be as simple or as appropriate as we think. We will encounter even more fascinating cases later as we take a critical look at the designation of male versus female and the expectations that go with it. In the meantime, we need to continue our discussion of motivation by considering how sex is both like and unlike other drives.

SEX AS A FORM OF MOTIVATION

To say that sex is a motivated behavior like hunger may be stating the obvious. But theorists originally had difficulty categorizing sex with other physiological drives because it does not fit the typical pattern of a homeostatic tissue need. If you fail to eat or if you cannot maintain body temperature within reasonable limits, you will die. But no harm will come from forgoing sex; sex ensures the survival of the species but not of the individual.

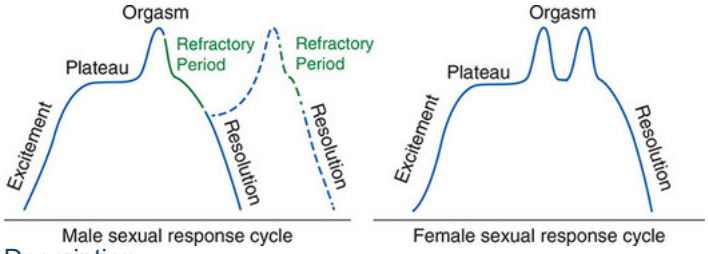
There are, however, important similarities with other drives such as hunger and thirst. They include arousal and satiation, the involvement of hormones, and control by specific areas in the brain. We will explore these similarities as well as some differences in the following pages.

Arousal and Satiation

The cycle of arousal and satiation is the most obvious similarity between sexual motivation and other motivated behaviors such as hunger and thirst. In the 1960s, William Masters and Virginia Johnson conducted groundbreaking research on the human sexual response. Until then, research had been limited to observing sexual behavior in animals or interviewing individuals about their sexual activity. Masters and Johnson (1966) observed 312 men and 382 women and recorded their physiological responses during 10,000 episodes of sexual activity in the laboratory. This kind of research was unheard of at the time; in fact, the researchers had to overcome significant social hurdles to conduct their research, and they had trouble finding journals willing to publish their work. Their work on human sexual behavior was the subject of the Showtime cable series *Masters of Sex*.

? How is sex like and unlike other drives?

Masters and Johnson (1966) identified four phases of sexual response (Figure 7.1). The *excitement phase* is a period of arousal and preparation for intercourse. Both sexes experience increased heart rate, respiration rate, blood pressure, and muscle tension. The male's penis becomes engorged with blood and becomes erect. The female's clitoris becomes erect as well, the labia swell and open, the vagina lubricates, the breasts enlarge, and the nipples become erect. While hunger is largely a function of time since the last meal, sexual arousal is more often influenced by opportunity and sexual stimuli, such as an explicit conversation or the presence of an attractive person. In contrast to humans, sexual arousal in most mammal species is triggered by a surge in hormones. Another difference between sex and other drives is that we usually are motivated to reduce hunger, thirst, and temperature deviations, but we seek sexual arousal. This difference is not unique, though; for example, we might skip lunch to increase the enjoyment of a gourmet dinner.



Description

Figure 7.1 Phases of the Sexual Response Cycle.
Males experience some amount of refractory period before they can have another orgasm (represented by dotted line). Females are capable of multiple orgasms.

Source: From Masters & Johnson, 1966.

During the *plateau phase*, the increase in sexual arousal levels off. Arousal is maintained at a high level for seconds or minutes, though it is possible to prolong this period. During this phase, the testes rise in the scrotum in preparation for orgasm and ejaculation; vaginal lubrication increases, and the vaginal entrance tightens on the

penis. During *orgasm*, rhythmic contractions in the penis are accompanied by ejaculation of seminal fluid containing sperm into the vagina. Similar contractions occur in the vagina. Orgasm is brief, but it involves an intense experience of pleasure; descriptions of this pleasure vary widely, ranging from “warmth” to “electricity.” (Masters and Johnson noted that some females have a prolonged plateau phase without orgasms.)

Orgasm is typically followed by *resolution*, which is reminiscent of the period of quiet after return to homeostasis with other drives. The muscles relax, blood pressure drops, and excitement decreases. Women are capable of having multiple orgasms before entering the resolution phase. Men may have a second orgasm soon after the first (dotted line in Figure 7.1), but inability to have another orgasm or even to become aroused is more typical. This refractory period can last for minutes, hours, or even days, depending on the individual and the circumstances. Women typically do not experience a refractory period; their inactivity following orgasm is more often attributed to lack of adequate stimulation, fatigue, or loss of interest. The refractory period has an interesting parallel with sensory-specific satiety (see Chapter 6). This phenomenon—the **Coolidge effect**, a quicker return to sexual arousal when a new partner is introduced—has been observed in a wide variety of species (see Dewsbury, 1981; J. R. Wilson, Kuehn, & Beach, 1963). Although the Coolidge effect occasionally occurs in females, it is less likely than in their male counterparts (Lester & Gorzalka, 1988).

Hormonal Control of Sexual Behavior

As important as sex is to humans, it is ironic that so much of what we know about the topic comes from the study of other species. One reason is that research into human sexual behavior was for a long time considered off-limits, and funding was hard to come by. Another reason is that sexual behavior is more “accessible” in nonhuman animals; rats have sex as often as 20 times per day and are not at all embarrassed to perform in front of the experimenter. In addition, we can manipulate their sexual behavior in ways that would be considered unethical with humans. Hormonal control in particular is more often studied in animals because hormones have a clearer role in animal sexual behavior.

Numerous hormones and neurotransmitters influence sexual behaviors and performance and gender-related characteristics; we will discuss four that are required for the majority of these. **Androgens** (a class of hormones responsible for a number of male characteristics and functions) are more abundant in males than in females. The androgen **testosterone** is the major sex hormone in males. Males produce 15 to 20 times more than females (Handelsman, Hirschberg, & Bermon, 2018), mostly in the testes (95%) but also in the adrenal glands (5%); females produce small amounts in their ovaries. **Estrogens**, a class of hormones responsible for a number of female characteristics and functions, are primarily produced by the ovaries in females, though the testes of males do produce a small amount. **Progesterone** (a member of the class progestogens) is also considered a female hormone, but it too is produced in the adrenal glands and testes of males, who need it to produce testosterone. In females, it controls reproductive functions, including sexual receptivity and desire (B. C. Jones et al., 2018; C. F. Yang et al., 2013). **Oxytocin** is both a hormone and a neuropeptide, produced by the hypothalamus and released by the pituitary; it promotes sexual arousal and social bonding and contributes to male and female orgasm and the intensity of its pleasure.

We have learned a great deal about the contributions of these substances, primarily through their removal and by studying the changes in sexual behavior that result. **Castration** (orchidectomy), or removal of the gonads (testes or ovaries), is one technique used to study hormonal effects because it removes the major source of sex hormones; castration results in a loss of sexual motivation in nonhuman mammals of both sexes. Sexual behavior may not disappear completely, because the adrenal glands continue to produce both male and female hormones, though at a lesser rate than the gonads. The time course of the decline is also variable, ranging from a few weeks to 5 months in male rats (J. M. Davidson, 1966); across several species, animals that are sexually experienced are impaired the least and decline the slowest

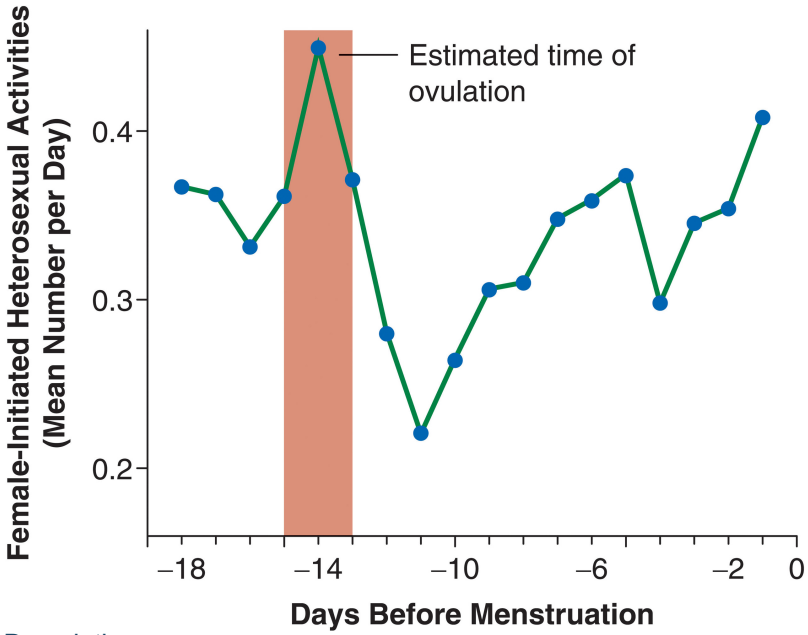
(Hart, 1968; Sachs & Meisel, 1994). Humans are less at the mercy of fluctuating hormone levels than other animals, but when they are castrated (usually for medical reasons, such as testicular or ovarian cancer), sexual interest and functioning decrease in both males and females (Bremer, 1959; Heim, 1981; Sherwin & Gelfand, 1987; Shifren et al., 2000). The decline takes longer in humans than in rats, but the rate is similarly variable.

Castration has been elected by some male criminals in the hope of controlling aggression or sexual predation, sometimes in exchange for shorter prison sentences. Castration is an extreme therapy; drugs that counter the effects of androgens are a more attractive alternative. Those that block the production of testosterone have been 80% to 100% effective in eliminating deviant sexual behavior, such as exhibitionism and pedophilia (sexual contact with children), along with sexual fantasies and urges (A. Rösler & Witztum, 1998; Thibaut, Cordier, & Kuhn, 1996). Chemical castration is either allowed on a voluntary basis or mandated for some offenses in nine states in the United States (Koo, Ahn, Hong, Lee, & Chung, 2014; M. Park, 2012) and in several other countries.

The effects of castration indicate that testosterone is necessary for male sexual behavior, but the amount of testosterone required appears to be minimal. Men with very low testosterone levels can be as sexually active as other men (Garelick & Swann, 2014; Raboch & Stárka, 1973). And individuals with **hypogonadism**, a disorder in which little or no hormones are produced by the ovaries or testes, exhibit reduced (but not absent) sexual behaviors (Shi, Araujo, Martin, O'Loughlin, & Wittert, 2013; Traish, 2017).

Frequency of sexual activity and testosterone levels do vary together *within* an individual, but the testosterone increases appear to be the *result* of sexual activity rather than the cause. Male rats show a sharp increase in testosterone levels when first presented with a receptive female, and the levels decrease on subsequent days of testing (Shulman & Spritzer, 2014). In human males, testosterone levels are high at the *end* of a period in which intercourse occurred, not necessarily before (Dabbs & Mohammed, 1992; Kraemer et al., 1976). There have also been occasional reports of male testosterone levels increasing in anticipation of sexual activity (Anonymous, 1970; J. M. Graham & Desjardins, 1980). The overwhelming evidence points to sex triggering testosterone increases, not the other way around.

In most mammals, females are unwilling to engage in sex except during **estrus**, a period when the female is ovulating, sex hormone levels are high, and the animal is said to be in heat. Human females and females of some other primate species engage in sex throughout the reproductive cycle. Studies of sexual frequency in women have not shown a clear peak at the time of ovulation. However, initiation of sex is a better gauge of the female's sexual motivation than is her willingness to have sex; women do initiate sexual activity more often during the middle of the menstrual cycle, which is when ovulation occurs (Figure 7.2; Adams, Gold, & Burt, 1978; S. M. Harvey, 1987). The researchers attributed the effect to estrogens. Their reasons were that estrogen level peaks at midcycle and that the women did not increase in sexual activity if they were taking birth control pills, which level out estrogen release over the cycle.

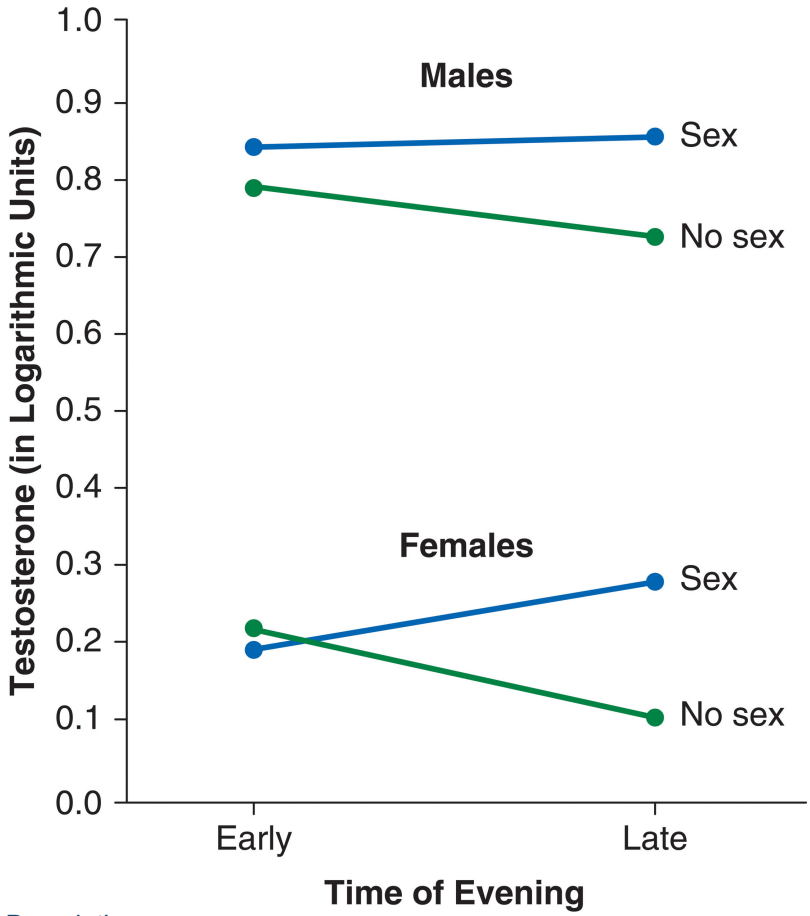


Description

Figure 7.2 Female-Initiated Sexual Activity During the Menstrual Cycle.
Activity initiated by women peaks around the middle of the menstrual cycle, which is when ovulation occurs.

Source: From figure 2 from "Rise in Female-Initiated Sexual Activity at Ovulation and Its Suppression by Oral Contraceptives," by D. B. Adams, A. R. Gold, and A. D. Burt, 1978, *New England Journal of Medicine, 299*(21), pp. 1145–1150.

However, testosterone peaks at the same time, and the frequency of intercourse during midcycle corresponds to the woman's testosterone level (N. M. Morris, Udry, Khan-Dawood, & Dawood, 1987). At menopause, when both estrogen and testosterone levels decline, testosterone levels show the most consistent relationship with intercourse frequency (McCoy & Davidson, 1985). How to interpret these observations is unclear, because testosterone increases in women as a *result* of sexual activity, just as it does in men (Figure 7.3; Dabbs & Mohammed, 1992). However, studies in which testosterone level was manipulated demonstrate that it also *contributes* to women's sexual behavior. Giving a dose of testosterone to women increases their arousal during an erotic film (Tuiten et al., 2000). More important, in women who had their ovaries removed, testosterone treatment increased sexual arousal, sexual fantasies, and intercourse frequency, but estrogen treatment did not (Sherwin & Gelfand, 1987; Shifren et al., 2000).



Description

Figure 7.3 Relationship Between Sexual Behavior and Salivary Testosterone Levels in Men and Women.

Source: From "Male and Female Salivary Testosterone Concentrations Before and After Sexual Activity," by J. M. Dabbs, Jr. and S. Mohammed, *Physiology and Behavior, 52*, pp. 195–197, Fig. 1. © 1992 Reprinted with permission from Elsevier Science.

This is not to say that testosterone is solely responsible for sexual desire in women; remember that we said earlier that progesterone is important. You are learning that no behavior can be attributed to a single hormone, a single gene, or a single part of the brain, and sexual behavior is no exception. A recent study has suggested that progesterone is correlated with sexual desire in women (B. C. Jones et al., 2018). Like estrogen and testosterone, progesterone declines with menopause, and it has been useful as a hormone replacement therapy. So as you can see, sexual behavior is influenced by multiple sex hormones.

Brain Structures and Neurotransmitters

As neuroscientists developed a clearer understanding of the roles of various brain structures, motivation researchers began to shift their focus from drive as a tissue need to drive as a condition in the brain. Sexual activity, like other drives and behaviors, involves a network of brain structures. This almost seems inevitable, because sexual activity involves reaction to a variety of stimuli, activation of several physiological systems, postural and movement responses, a reward experience, and so on. We do not understand yet how the sexual network operates as a whole, but we do know something about the functioning of several of its components. In this section, you will see some hypothalamic structures you're familiar with from Chapter 6. This

illustrates an important principle of brain functioning: Brain areas, even very small ones, often have multiple functions. The most important ones for sexual behaviors are summarized in Table 7.1.

Table 7.1

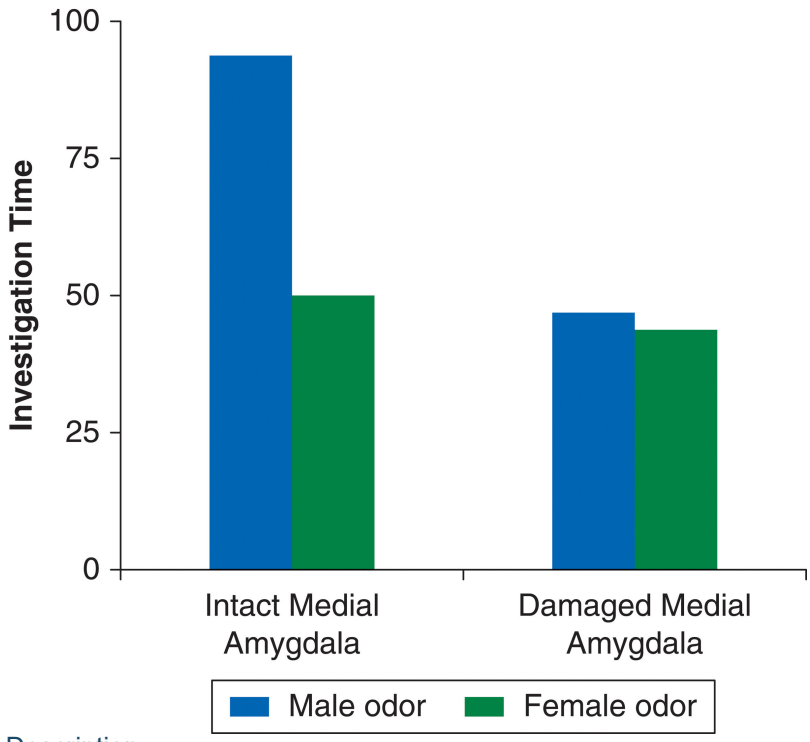
TABLE 7.1 Brain Areas Implicated in Sexual Behaviors.

BRAIN AREA	SEX	IMPLICATED BEHAVIORS
Medial preoptic area (MPOA)	Both	Copulation; sexual performance as opposed to motivation
Ventromedial hypothalamus (VMH)	Both	Female receptivity; male vigor in mating
Medial amygdala	Both	Response to sexually exciting stimuli, including odors
Paraventricular nucleus (PVN)	M	Sexual performance, including penile erection
Sexually dimorphic nucleus (SDN)	M > F	Integrates sensory and hormonal information to coordinate responses to sexual cues

Some areas are important in sexual behavior in both sexes. The **medial preoptic area (MPOA)** is one of the more significant brain structures involved in male and female sexual behavior. (Be careful not to confuse the medial preoptic area with the median preoptic nucleus, discussed in Chapter 6. They are both in the preoptic area, which you can locate in Figure 6.2.) Stimulation of the MPOA increases copulation in rats of both sexes (Bloch, Butler, & Kohlert, 1996; Bloch, Butler, Kohlert, & Bloch, 1993), and it is active when they copulate spontaneously (Pfaus, Kleopoulos, Mobbs, Gibbs, & Pfaff, 1993; Shimura & Shimokochi, 1990). Opiates such as oxycodone and heroin reduce activity in the MPOA and therefore impair sexual behavior (Band & Hull, 1990). The MPOA appears to be more responsible for performance than for sexual motivation; when it was destroyed in male monkeys, they no longer tried to copulate, but instead they would often masturbate in the presence of a female (Slimp, Hart, & Goy, 1978). The **ventromedial hypothalamus (VMH)** is important for sexual interest and motivation in both males and females. Its ablation reduces female receptivity to males' advances and the vigor of the male's mating behavior (see Figure 6.2; C. F. Yang et al., 2013).

? What brain structures are involved in sexual behavior?

The **medial amygdala** also contributes to sexual behavior in animals of both sexes. (We will talk more about the amygdala's role in emotions and aggression in Chapter 8.) The medial amygdala is active while rats copulate (Pfaus et al., 1993), and stimulation causes the release of dopamine in the MPOA (Dominguez & Hull, 2001; Matuszewich, Lorrain, & Hull, 2000). The medial amygdala's role apparently is to respond to sexually exciting stimuli, such as the presence of a potential sex partner (de Jonge, Oldenburger, Louwerse, & Van de Poll, 1992). For example, it is needed for recognizing individuals of the opposite sex by their odors (Figure 7.4; Petrulis & Johnston, 1999).

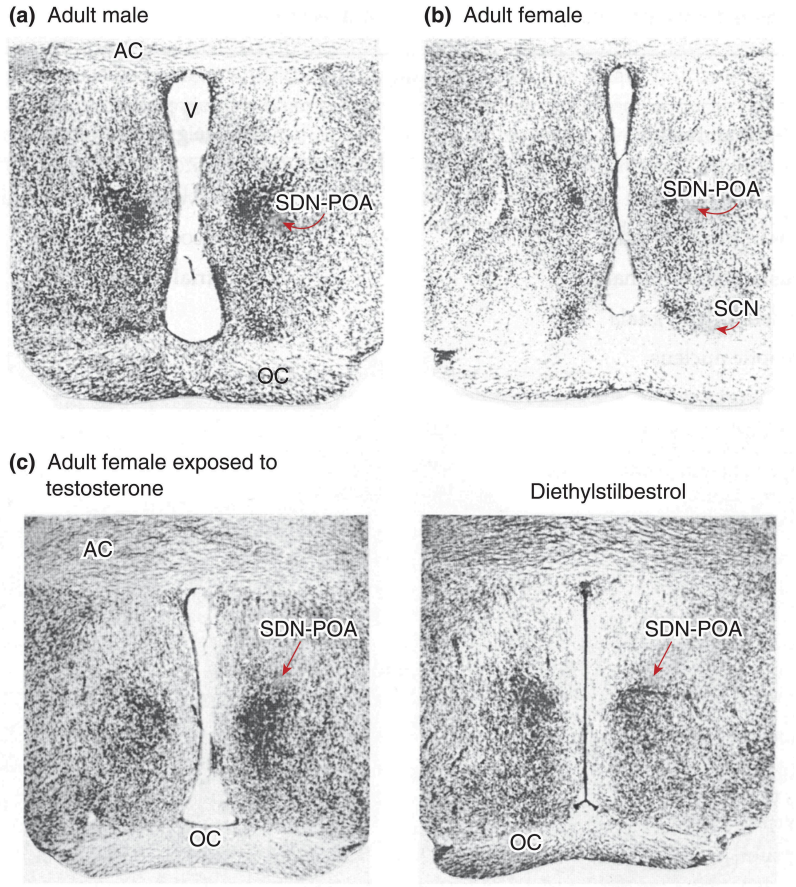


Description

Figure 7.4 Amount of Time Female Hamsters Investigated Male Odors or Female Odors.
Intact females (with sham surgery that left the amygdala undamaged) spent more time investigating male odors than female odors; after damage to the medial amygdala, they no longer showed a particular interest in male odors.

Source: Adapted from "Lesions centered on the medial amygdala impair scent-marking and sex-odor recognition but spare discrimination of individual odors in female golden hamsters" by A. Petrulis and R. E. Johnston, *Behavioral Neuroscience, 113,* p. 350. © 1999 American Psychological Society. Reprinted with permission.

A few areas are involved in sexual behaviors of one sex but not the other. The paraventricular nucleus (PVN) is important for male sexual performance and particularly for penile erections, due to effects of oxytocin there (see Figure 6.2; Argiolas & Melis, 2004). Especially significant for males is the **sexually dimorphic nucleus (SDN)**, located in the preoptic area. The SDN is three to four times larger in male rats than in females, and a male's level of sexual activity is related to the size of the SDN (Figure 7.5; de Jonge et al., 1989; He, Ferguson, Cui, Greenfield, & Paule, 2013). The size in turn depends, at least in part, on protection by testosterone from the cell death that occurs during the pruning stage shortly after birth (He et al., 2013). Destruction of the SDN reduces male sexual activity (de Jonge et al.). The SDN's connections to other sex-related areas of the brain suggest that it integrates sensory and hormonal information and coordinates behavioral and physiological responses to sensory cues (Roselli, Larkin, Resko, Stellflug, & Stormshak, 2004).



Description

Figure 7.5 The Sexually Dimorphic Nuclei of the Rat.
(a) The SDN in the male is larger than (b) the SDN in the female. (c) The effects of testosterone and a masculinizing synthetic hormone on the female SDN.

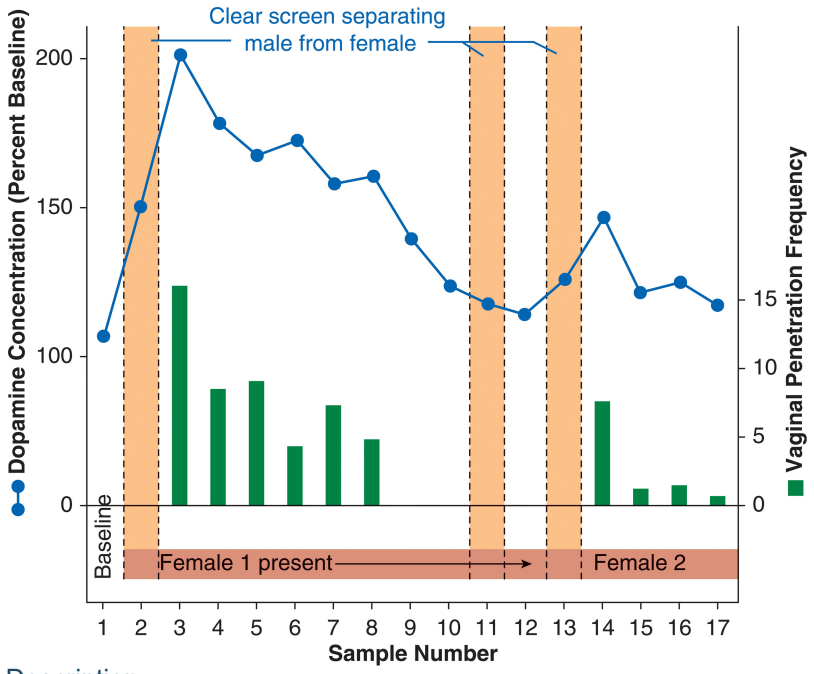
Source: From "The Neuroendocrine Regulation of Sexual Behavior," by R. A. Gorski, pp. 1–58, in G. Newton and A. H. Riesen (Eds.) *Advances in Psychobiology* (Vol. 2), 1974, New York: Wiley. Reprinted with permission of John Wiley & Sons, Inc.

For obvious reasons, we know much less about the brain structures involved in human sexual behavior. Functional MRI (fMRI) recording during masturbation has confirmed the involvement of the medial amygdala and PVN in human sexual activity (Komisaruk et al., 2004). PVN neurons secrete oxytocin, which is involved in sexual performance and pleasure. We also know that a few brain structures in humans differ in size between males and females. Because their contribution to sexual behavior is not clear and the size differences may also distinguish gay individuals rom heterosexuals, we will defer discussion of these structures until we take up the subject of sexual orientation.

Sexual behavior involves several neurotransmitters, but dopamine has received the most attention. Aside from its rewarding effects in the nucleus accumbens (see Chapter 5), dopamine plays a significant role in sexual motivation and performance. As we noted earlier, stimulation of the medial amygdala releases dopamine in the MPOA, enabling the individual to respond to sexually exciting stimuli. In males, dopamine is critical for sexual performance: At moderate levels, dopamine increases motivation and erection by stimulating D_1 receptors and increasing parasympathetic activation; as the dopamine level continues to increase, it activates D_2 receptors and shifts autonomic balance to the sympathetic system, resulting in orgasm and ejaculation. D_2 activity also inhibits erection, which probably accounts in part for the

sexual refractory period in males. The dopamine system has been reported to be active in the ventral tegmental area in males during ejaculation (Holstege et al., 2003) and in the nucleus accumbens in females during orgasm (Komisaruk et al., 2004). This activity likely reflects a reward response, but the activated areas also contribute motor output to the pelvic floor muscles, producing the contractions that are characteristic of orgasm.

Drugs that increase dopamine levels, such as stimulants and those used in treating Parkinson's disease, increase sexual activity (Evans, Haney, & Foltin, 2002; Meston & Frohlich, 2000). Variations in the gene for the D_4 receptor (*DRD4*) have been associated with sexual arousal, experimentation, and promiscuity (Ben Zion et al., 2006; Halley, Boretsky, Puts, & Shriver, 2016). Interestingly, dopamine release parallels sexual behavior during the Coolidge effect. As you can see in Figure 7.6, it increased in the male rat's nucleus accumbens in the presence of a female, dropped back to baseline as interest waned, and then increased again with a new female (Fiorino, Coury, & Phillips, 1997). The changes occurred even when the male and female were separated by a clear panel, so the dopamine level reflects the male's interest rather than the effects of sexual activity.



Description

Figure 7.6 Dopamine Levels in the Nucleus Accumbens During the Coolidge Effect. Activity was recorded until the male lost interest in Female 1; then, Female 2 was presented. During the periods represented by the orange bars, the female was separated from the male by a clear screen. The line graph shows dopamine levels. Bars show the number of vaginal penetrations.

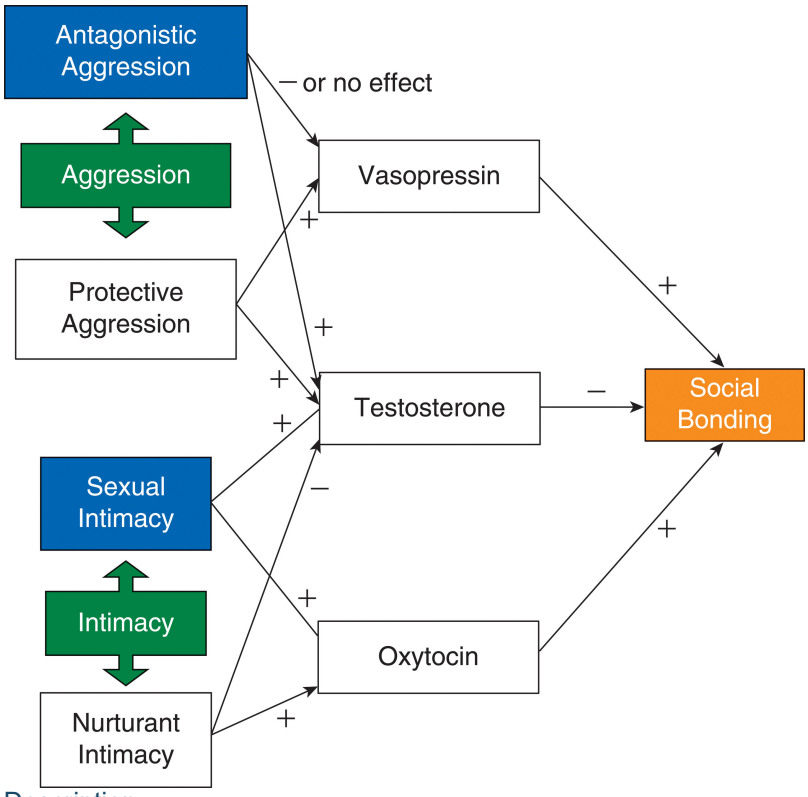
Source: From "Dynamic Changes in Nucleus Accumbens Dopamine Efflux During the Coolidge Effect in Male Rats," by D. F. Fiorino, A. Coury, and A. G. Phillips, 1997, *Journal of Neuroscience*, 17, p. 4852. © 1997 Society for Neuroscience. Reprinted with permission.

In contrast to the stimulatory activity of dopamine, serotonin has a primarily inhibitory effect on sexual behaviors in both males and females (Croft, 2017; E. M. Hull, Muschamp, & Sato, 2004). Selective serotonin reuptake inhibitors (SSRIs) increase serotonin at synapses; injecting an SSRI into the MPOA decreases sexual motivation in animals, and injection into the lateral hypothalamus lengthens the time between copulations and their ability to ejaculate when they do return to sexual activity. Serotonin increases in the lateral hypothalamus during ejaculation, which apparently contributes to the refractory period (E. M. Hull et al., 2004). Serotonin release can

also cause a drop in dopamine levels, which further prevents arousal and might add to the refractory period (Lorrain, Riolo, Matuszewich, & Hull, 1999). Hallucinogenic drugs such as LSD, DMT, and mescaline (which are structurally similar to serotonin) also can interfere with sexual behaviors. People who take SSRIs to treat their anxiety or depression often complain that the drugs interfere with their sexual performance. The antianxiety drug buspirone, by contrast, decreases the release of serotonin and facilitates orgasms (Komisaruk, Beyer, & Whipple, 2008). But like all things involving the brain, it gets complicated: At low levels, some serotonin agonists can have a stimulatory effect on sexual behaviors by stimulating other serotonin receptor subtypes (Gorzalka, Mendelson, & Watson, 1990).

Oxytocin contributes to bonding and causes the smooth muscle contractions involved in male and female orgasm as well as milk ejection during breastfeeding. In humans, blood levels of oxytocin increase as males and females masturbate to orgasm, and oxytocin release correlates with the intensity of pleasure (Carmichael, Warburton, Dixen, & Davidson, 1994; M. R. Murphy, Checkley, Seckl, & Lightman, 1990).

An interesting model for the regulation of gender-related aggressive and bonding behaviors has been proposed in the steroid/peptide theory of social bonds (van Anders, Goldey, & Kuo, 2011). According to this theory, the balance among testosterone, oxytocin, and vasopressin determine behaviors such as aggression and intimacy (Figure 7.7). As you probably guessed, a high testosterone level in either sex increases aggression, but it also impairs the formation of close social bonds. Oxytocin (involved in muscle contractions of sexual tissue and in social bonding) and vasopressin (a potent neuromodulator of brain activity) modulate the form of intimacy and aggression. Antagonistic aggression (which includes social dominance, partner acquisition, and defense of partners and territory) is seen in those with low levels of vasopressin, whereas protective aggression (such as defending children or partners) is seen in those with high levels of vasopressin. Intimacy increases oxytocin, but its interaction with testosterone levels determines whether that intimacy is sexual (if testosterone is high) or nurturing (if testosterone is low). Therefore, testosterone levels determine the relative amount of competitive versus nurturing behaviors that an individual expresses, whereas oxytocin determines the relative amount of social bonding versus social isolation.



Description

Figure 7.7 The Steroid/Peptide Theory of Social Bonds.
In this theory, three important hormones interact to determine not only the strength of bonds with others but also the characteristics of those relationships. First, testosterone levels increase aggression and decrease social bonding, while vasopressin levels modify the form of aggression. Low levels of vasopressin cause attack-type behaviors (antagonistic), while high levels of vasopressin increase protective behaviors that result in stronger social bonds with others. Oxytocin regulates the level of intimacy and interacts with testosterone as well. Low testosterone with high oxytocin is correlated with more helpful, supporting intimacy and stronger social bonds, whereas high levels of both hormones lead to more sexualized relationships with others. Therefore, the strongest social bonds result from high levels of oxytocin and vasopressin and low levels of testosterone.

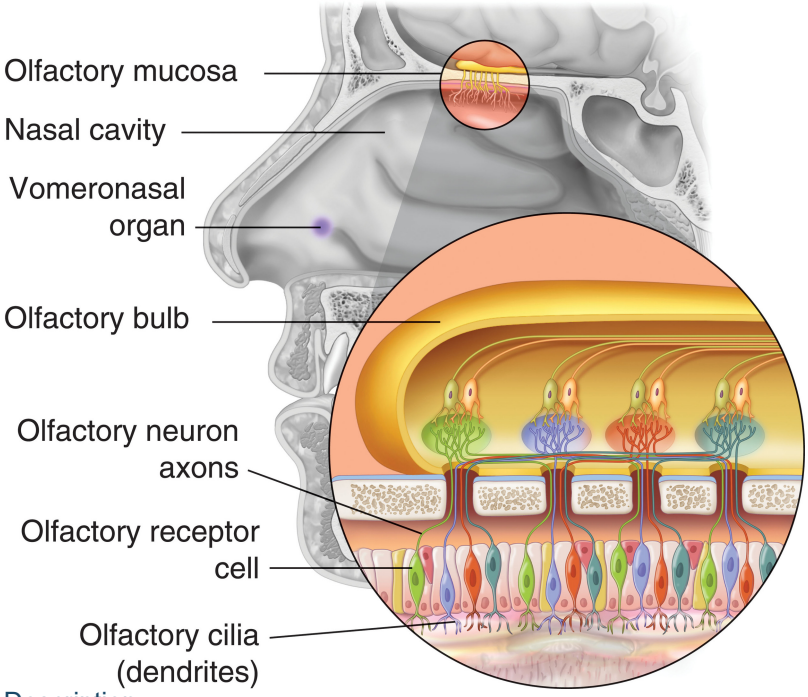
Source: From "The Steroid/Peptide Theory of Social Bonds: Integrating testosterone and peptide responses for classifying social behavioral contexts," by S. M. van Anders, K. L. Goldey, & P. X. Kuo. *Psychoneuroendocrinology*, 36(9). © Elsevier. Reprinted with permission.

Odors, Pheromones, and Sexual Attraction

Sexual behavior results from the interplay of internal conditions, particularly hormone levels, with external stimuli. Sexual stimuli can be anything from brightly colored plumage or an attractive body shape to specific odors. Here we will examine the role of odors and pheromones in sexual attraction, with emphasis on how important they might be for humans.

Before we launch into this discussion, we need to have a basic understanding of the olfactory (smell) system. Olfaction is one of the two chemical senses, along with taste. Airborne odorous materials entering the nasal cavity must dissolve in the mucous layer overlying the receptor cells; the odorant then stimulates a receptor cell when it binds to receptor sites on the cell's dendrites (Figure 7.8). Axons from the olfactory receptors pass through openings in the base of the skull to enter the

olfactory bulbs, which lie over the nasal cavity. From there, neurons follow the olfactory nerves to the nearby olfactory cortex tucked into the inner surfaces of the temporal lobes.



Description

Figure 7.8 The Olfactory and Vomeronasal Systems.

By varying the number of components in odor mixtures, researchers have calculated that humans can distinguish approximately a trillion odors (Bushdid, Magnasco, Vosshall, & Keller, 2014). We obviously do not have a different receptor for each odor; the brain must rely on the combination of receptors activated to distinguish among so many different stimuli. Humans have around 400 different receptor genes that produce an equal number of receptor types, and additional alleles of some of these genes brings the total to about 600 (Olender et al., 2012). The greater numbers of genes in other animals—800 in dogs, 1,100 in mice, and 2,000 in the African elephant (Niimura, Matsui, & Touhara, 2016)—along with "common knowledge," have been used to argue that humans have poorly developed olfactory capability. Yet humans can follow a scent trail across a grassy field (Porter et al., 2007), and actual comparisons show that humans have higher sensitivity with most odorants and only slightly inferior discrimination ability compared to the majority of mammal species tested so far (Laska, 2017).

There is a good argument to be made for the nose as a sexual organ. The most convincing evidence comes from the study of **pheromones**, airborne chemicals released by an animal that have physiological or behavioral effects on another animal of the same species. In nonhuman animals, most pheromones are detected by the **vomeronasal organ (VNO)**, a cluster of receptors also located in the nasal cavity. The VNO is illustrated in Figure 7.8, although you will soon see that most researchers believe that it is no longer functional in humans, the victim of evolution as our ancestors developed color vision and came to rely on visual sexual signals (I. Rodriguez, 2004). The VNO's pathway leads to the MPOA and the ventromedial nucleus of the hypothalamus, as well as to the amygdala (Keverne, 1999). The VNO and olfactory systems are neurally separate (P. J. Hines, 1997), and the VNO's receptors are produced by a different family of genes. Less than 10% of one of the two major classes of pheromone genes is active in humans, and the other class has not been found in humans (Touhara & Vosshall, 2009). However, a VNO may not be entirely necessary, because some pheromones and pheromone-like odors can be

detected by the olfactory system when an animal's VNO has been blocked or surgically eliminated (Wysocki & Preti, 2004).

Pheromones can be very powerful, as you know if your yard has ever been besieged by all the male cats in the neighborhood when your female cat was in heat. The female gypsy moth can attract males from as far as 2 miles away (Hopson, 1979). Pheromones provide cues for kin recognition in animals, influence cycling of sexual receptivity in female mice, initiate aggression in both males and females, and trigger maternal behavior in adults and suckling in infants (Wysocki & Preti, 2004). Male pigs exude androstenone, which elicits sexual posturing and receptivity in females; pig farmers use androstenone as an aid during artificial insemination. Perhaps the most dramatic example is the Bruce effect. Females of several species, from mice to monkeys, will abort a pregnancy when they are exposed to the urine of a strange male. It is thought to have evolved as a response to the threat of infanticide by the intruder (Eccard, Dammhahn, Ylönen, 2017).

So do pheromones play a role in human behavior? The general consensus is that the VNO is nonfunctional in humans; according to James Cherry and Michael Baum (2019), pheromones affect humans by means of the olfactory system and its pathway to the medial amygdala, which in turn activates sexual regulatory sites in the hypothalamus. They point out that men who have lost the sense of smell (anosmia) have fewer sexual partners and that anosmic women report a reduction in "partnership security"; in women, there is also a correlation between olfactory sensitivity and the rated pleasantness of sexual intercourse. Two compounds have been identified as possible human pheromones: androstadienone (AND), a steroid found in male sweat, and estratetraenol (EST), a steroid found in female urine. In studies in which women smelled AND, their cortisol levels increased, and they reported more positive mood and greater sexual arousal. Likewise, EST has been reported to increase men's sexual arousal, their accuracy in judging interpersonal relations, and their cooperation in a competitive task.

But these studies and others have been criticized on methodological grounds and have often failed replication, to the point that the idea of pheromonal control of human behavior is highly controversial. An often-cited study reported that EST produced increased activity in the MPOA in heterosexual men and that AND activates the SDN in heterosexual women and gay men (Savic, Berglund, & Lindström, 2005). However, this study has been criticized for using compounds at a million times their natural concentration; at normal concentration, the results were contradictory (Wyatt, 2015). And if you've heard that women living together synchronize their menstrual cycles through some form of pheromone release, later research failed to support the studies (Z. Yang & Schank, 2006).

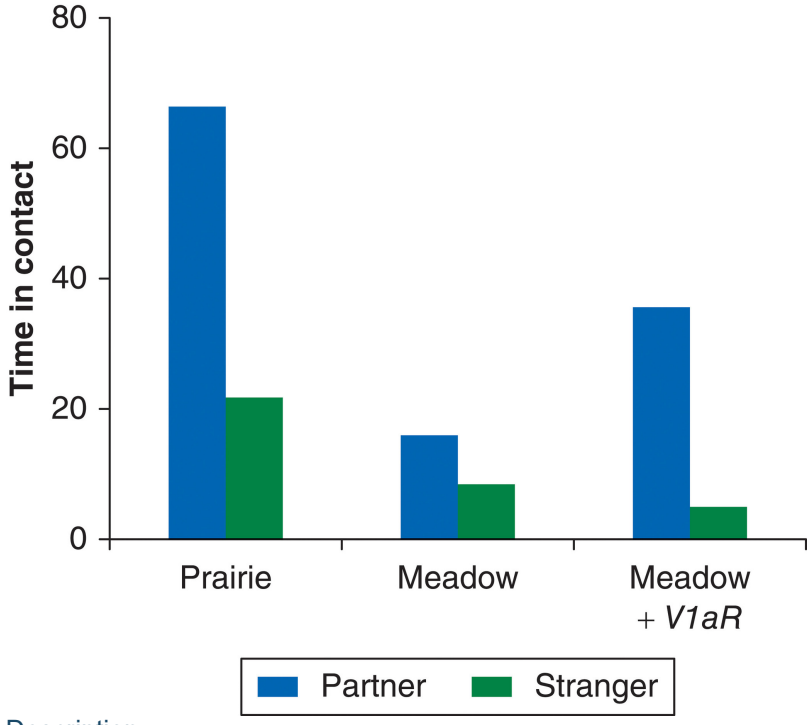
? Is there evidence for pheromones in human sexual behavior?

A source of body odors that influence mating behavior in animals is the major histocompatibility complex (MHC), a group of genes that encode proteins that help the immune system detect foreign proteins. Fish, birds, and mammals prefer mates with dissimilar MHC genes, which provides offspring with broader disease resistance. Studies suggest that human couples with greater MHC dissimilarity report more sexual satisfaction and that women partnered with a MHC-dissimilar male rate the partner's body odor more favorably and are more likely to want to have children with the partner (Kromer et al., 2016). These studies have met the same fate as pheromone research, with contradictory results and criticism of research methodology. The bottom line is that we are not yet in a position to draw conclusions about either pheromone or MHC influence on human sexual behavior. Translating animal research results into the human domain can be extremely difficult, especially when sexual behavior and mate choice are involved.

In most animals, attraction is fleeting, lasting only through copulation or, at best, until the end of the mating season. For a few species, though, pair bonding occurs for years or for a lifetime, as we see in A Further Look.

A Further Look:

Of Love, Bonding, and Empathy



Description

Source: Adapted from Figures 1a–f, 2a, and 3a from "Enhanced Partner Preference in a Promiscuous Species by Manipulating the Expression of a Single Gene," by M. M. Lim, Z. Wang, D. E. Olazábal, X. Ren, E. F. Terwilliger, and L. J. Young, *Nature,* Vol. 429, pp. 754–757. Reproduced with permission from Nature Publishing Group.

Prairie voles, unlike 97% of mammals, are monogamous; they mate for life, and if they lose a mate, they rarely take another partner. The bonding process (reviewed in L. J. Young & Wang, 2004) begins with the release of dopamine in reward areas during mating. If dopamine activity is blocked by a receptor antagonist, partner preference fails to develop. Sexual activity also releases the neuropeptides oxytocin and vasopressin, which are likewise required for bonding to take place. Either can facilitate bonding in males or females, though oxytocin is more effective with females and vasopressin with males. Prairie voles have large numbers of vasopressin receptors, while meadow voles, a closely related species that is polygamous, do not (b). Miranda Lim and her colleagues (2004) at Emory University injected male meadow voles with the prairie vole *V1aR* gene, and within 2 weeks, they had developed numerous vasopressin receptors (c). After mating with a female for 24 hours, they had bonded with the partner, spending more contact time "huddling" with her than with a stranger (d).

So does any of this apply to humans, who are also monogamous (more or less)? The most apparent parallel involves oxytocin. Oxytocin levels are higher in new lovers than in singles, are correlated with romantic behaviors such as affectionate touching, and predict which partners will be together 6 months later (Schneiderman, Zagoory-Sharon, Leckman, & Feldman, 2012). Males are better at recognizing previously seen photos of women after receiving oxytocin via nasal spray (Rimmele, Hediger, Heinrichs, & Klaver, 2009). Oxytocin also increased activity in the nucleus accumbens of men while viewing photos of their partners and increased their ratings of their partners' attractiveness, but not of other women they knew (Scheele et al., 2013).

Oxytocin's bonding effects are not limited to mates and sex partners. Oxytocin also apparently explains empathetic behavior in prairie voles. Though we can't speculate about what the rodents are "feeling," they respond to a fear-stressed cagemate with increased grooming, and they match the cagemate's fear response, anxiety-related behaviors, and corticosterone increase (Burkett et al., 2016). Consoling behavior did not occur if the animals were given an infusion of an oxytocin receptor antagonist into the lateral ventricles.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

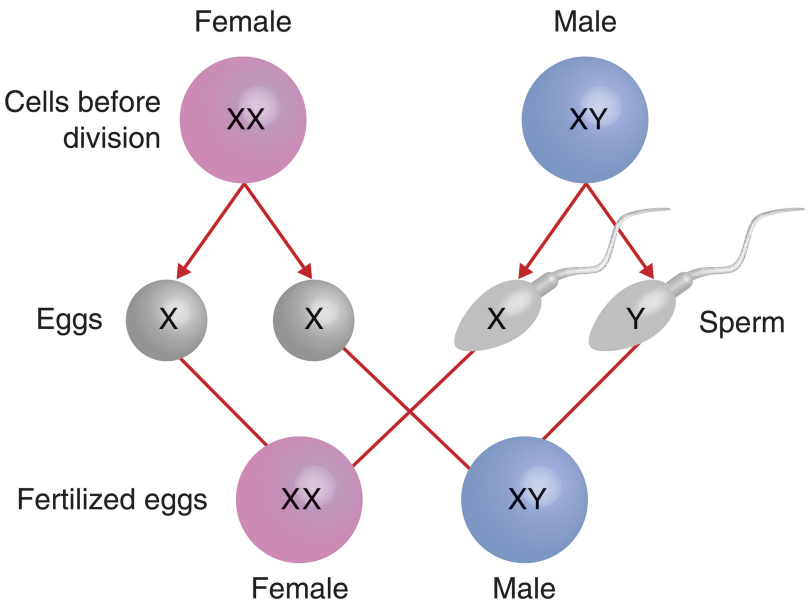
- What change in thinking helped researchers see sex as similar to other biological drives?
- What roles do estrogen and testosterone play in sexual behavior in humans?
- What roles do odors and pheromones play in animal and human sexual behavior?

THE BIOLOGICAL DETERMINATION OF SEX

Now we need to talk about differences between the sexes and the anomalies (exceptions) that occur. **Sex** is the term for the biological characteristics that divide humans and other animals into the categories of male and female. **Gender** refers to the behavioral characteristics associated with being male or female. For our purposes, it will be useful to make two further distinctions: **Gender role** is the set of behaviors society considers appropriate for people of a given biological sex, whereas **gender identity** is the person's subjective feeling of being male, female, a combination, or genderless. The term *sex* cannot be used to refer to all these concepts, because the characteristics are not always consistent with each other. Thus, classifying a person as male or female can sometimes be difficult. You might think that the absolute criterion for identifying a person's sex would be a matter of genitalia or chromosomes, but you will soon see that it is not that simple.

Chromosomes and Hormones

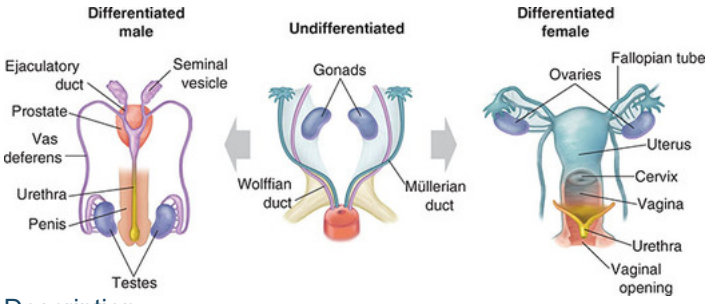
You may remember from Chapter 1 that when cells divide to produce sex cells, the pairs of chromosomes separate, and each gamete—the sperm or egg—receives only 23 chromosomes. This means that a sex cell has only one of the two sex chromosomes. In mammals, an egg will always have an X chromosome, but a sperm may have either an X chromosome or a Y chromosome. The procreative function of sexual intercourse is to bring the male's sperm into contact with the female's egg, or *ovum*. When the male ejaculates into the female's vagina, the sperm use their tail-like flagella to swim through the uterus and up the fallopian tubes, where the ovum is descending. As soon as one sperm penetrates and enters the ovum, the ovum's membrane immediately becomes impenetrable, so that only that sperm is allowed to fertilize the egg. The sperm makes its way to the nucleus of the ovum, where the two sets of chromosomes are combined into a full complement of 23 pairs. After fertilization, the ovum begins dividing, producing the billions of cells that make up the human fetus. If the sperm that fertilizes the ovum carries an X sex chromosome, the fetus will develop into a female; if the sperm's sex chromosome is Y, the child will be a male (Figure 7.9).



Description

Figure 7.9 Female and Male X and Y Chromosomes.

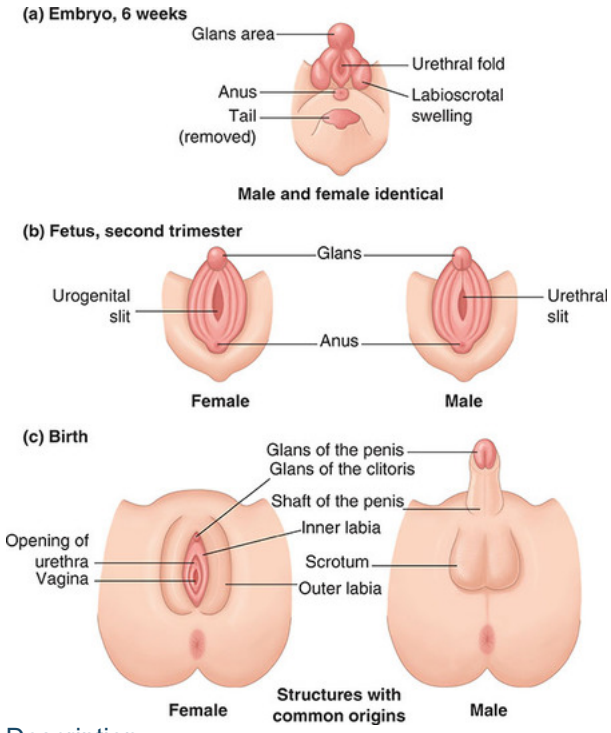
For the first month, XX and XY fetuses are identical. Later, the primitive (or indifferent) **gonads** (testes and ovaries, the primary reproductive organs) in the XX individual develop into **ovaries**, where the ova (eggs) will eventually develop. The **Müllerian ducts** develop into the uterus, the fallopian tubes, and the inner vagina, while the Wolffian ducts, which would become the male organs, wither and are absorbed (Figure 7.10). The undifferentiated external genitals become the clitoris, the outer segment of the vagina, and the labia, which partially enclose the entrance to the vagina (Figure 7.11).



Description

Figure 7.10 Development of Male and Female Internal Organs.

Source: Adapted from *Our Sexuality* (7ed.), by R. Crooks and K. Baur, 1999, Fig. 3.2 p. 46. Stamford, CT: Cengage Learning.



Description

Figure 7.11 Differentiation of Male and Female Genitals.

Source: Based on Netter (1983).

? What makes a person male or female?

If the fetus receives a Y chromosome from the father, the *SRY* (sex-determining region Y) gene on that chromosome produces a protein that causes the primitive gonads to develop into **testes**, the organs that will produce sperm. The testes begin secreting two types of hormones (Haqq et al., 1994). **Müllerian inhibiting hormone** defeminizes the fetus by causing the Müllerian ducts to degenerate. Testosterone, the most prominent of the androgens, masculinizes the internal organs: The **Wolffian ducts** develop into the seminal vesicles, which store semen, and the vas deferens, which carry semen from the testes to the penis. A derivative of testosterone, **dihydrotestosterone**, masculinizes the external genitals. The same structures that produce the clitoris and the labia in the female become the penis and the scrotum, into which the testes descend during childhood. In the absence of a Y chromosome (including the *SRY* gene), the primitive gonads of the XX fetus develop into ovaries. The ovaries won't begin producing estrogens until later, but in most mammals, the default sex is female, and the uterus, vagina, clitoris, and labia will all develop without benefit of hormones (Jost, 1953). You should understand that it is not entirely accurate to speak of hormones as being "male" or "female." We have already seen that both males and females secrete androgens and estrogens, although in differing amounts.

The hormonal effects we have been discussing are called organizing effects. **Organizing effects** mostly occur prenatally and shortly after birth; they affect structure, are lifelong in nature, and do not disappear when the hormone is removed. Organizing effects are not limited to the reproductive organs; they include sex-specific changes in the brains of males and females as well. **Activating effects** can occur at any time in the individual's life; they are reversible changes that can come and go as hormone levels change. Some of the changes that occur during puberty are examples of activating effects.

During childhood, differences between boys and girls other than in the genitals are relatively minimal. Boys tend to be heavier and stronger, but there is considerable overlap. Boys also are usually more active and more aggressive, and interests diverge at an early age (though admittedly much of this may be driven by how individuals are reared). Marked differences appear about the time the child enters puberty, usually during the preteen years. At puberty, a surge of estrogens from the ovaries and testosterone from the testes completes the process of sexual differentiation that began during prenatal development. Organizing effects include maturation of the genitals and increases in body size. Activating effects include breast development in the girl and muscle increases and hair growth in the boy. In addition, the girl's ovaries begin releasing the ova that have been there since birth (i.e., she begins to *ovulate*), and she starts to menstruate. Boys' testes start producing sperm, and ejaculation becomes possible. More important from a behavioral perspective, sexual interest increases dramatically, and in the majority of cases, preference for same-sex company shifts to an attraction to the other sex, along with an interest in sexual intimacy.

Prenatal Hormone Influences on Brain and Behavior

Several characteristics and behaviors can be identified as male typical and others as female typical. This does not mean that the behaviors are somehow more appropriate for that sex but simply that they occur more frequently in one sex than in the other. These differences are not absolute. For example, consider the stereotypical sexual behavior of rats: The male mounts the female from behind, while the female curves her back and presents her hindquarters in a posture called *lordosis*. However, females occasionally mount other females, and males will sometimes show lordosis when approached by another male.

The same hormonal influence responsible for the development of male gonads and genitals affects behavior as well. A male rat will display lordosis and accept the sexual advances of other males if he was castrated shortly after birth or if he was given a chemical that blocks androgens just before birth and for a short time postnatally (after birth). Similarly, a female rat given testosterone during this critical period will mount other females at a higher rate than usual as an adult (Figure 7.12; Gorski, 1974). These behaviors apparently result from the influence of testosterone on the size and function of several brain structures; in other words, the presence of testosterone masculinizes certain brain structures. That statement is somewhat misleading, though, because it is *estradiol*, the principal estrogen hormone, that carries out the final step of masculinization. When testosterone enters a neuron, it is converted to estradiol by a chemical process called *aromatization* (Figure 7.13). At the critical time when brain masculinization occurs, aromatase increases in the areas that are to be masculinized (Horvath & Wikler, 1999). To demonstrate the importance of estrogen for male-specific copulatory behavior, scientists were able to restore male-typical mounting behavior in castrated male rats that were given estrogen supplements (Vagell & McGinnis, 1997).

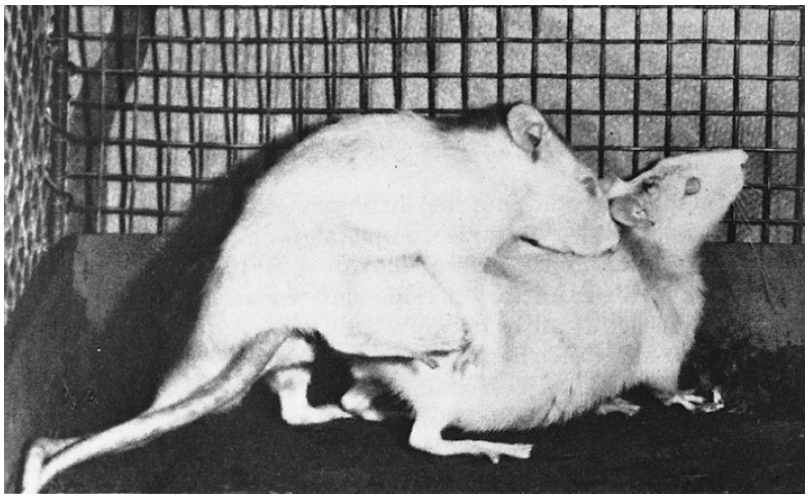
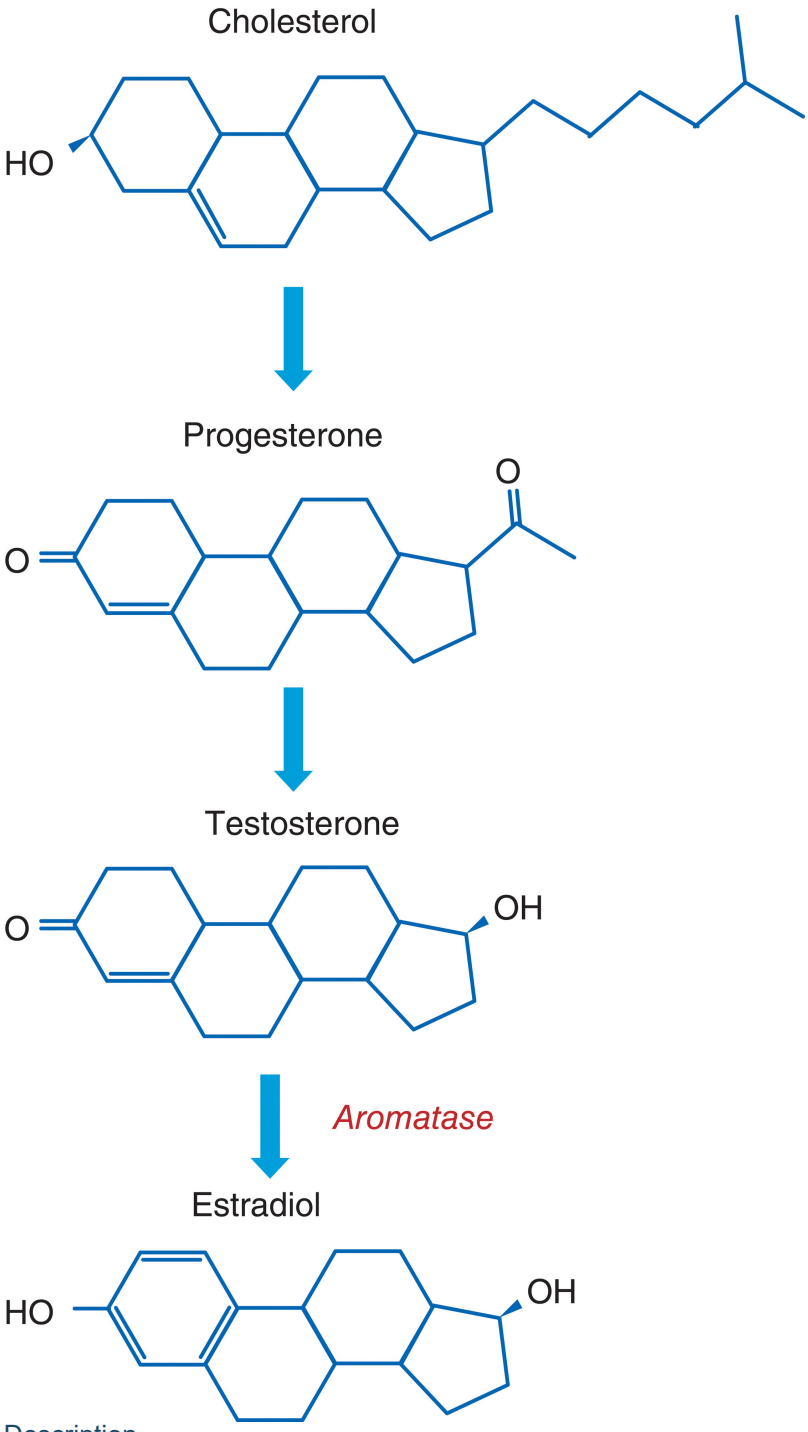


Figure 7.12 A Testosterone-Implanted Female Rat Mounting a Castrated Male Exhibiting Lordosis.

Source: From “Sex-Hormone-Dependent Brain Differentiation and Sexual Functions,” in G. Dörner (Ed.), *Endocrinology of Sex* (pp. 30–37). Leipzig: J. A. Barth. Copyright © 1974 Gunther Dörner. Used with permission.



Description

Figure 7.13 Biotransformation of Cholesterol to Testosterone and Estradiol. Cholesterol is the precursor to steroid hormones, including androgens and estrogens. Males convert cholesterol to testosterone, while females (and males, in some tissues) perform an additional conversion to estradiol using an aromatase enzyme.

? What is the effect of “sexualizing” the brain?

Until recently, it was believed that feminization of the brain, like the sex organs, required only the absence of testosterone; now we know that just as masculinization

of the male brain requires estradiol, so does feminization of the female brain. Female knockout mice born unable to produce estradiol display less sexual interest and receptivity toward males or females as adults than do other mice, even when they are given replacement estrogens (Bakker, Honda, Harada, & Balthazart, 2002, 2003). Just as the male brain must be masculinized and the female brain feminized, the male brain must also be defeminized. Again, estrogens are necessary; male knockout mice lacking the estrogen receptor showed normal male sexual behavior but also were receptive to advances of other males (Kudwa, Bodo, Gustafsson, & Rissman, 2005).

This sexualization of the brain is reflected in behavioral differences, affecting not only sexual activity but also play behavior, spatial activity, and learning performance (see Collaer & Hines, 1995). We will explore those influences in the following pages.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- How is the sex of a fetus determined, and what affects prenatal and postnatal sexual development?
- Distinguish between sex, gender, gender role, and gender identity.
- What effects do sex hormones have on differentiation of the brain and behavior?

GENDER-RELATED BEHAVIORAL AND COGNITIVE DIFFERENCES

In his popular book *Men Are From Mars, Women Are From Venus*, John Gray (1992) said that men and women communicate, think, feel, perceive, respond, love, and need differently, as if they are from different planets and speaking different languages. How different are men and women? This question is not easily answered, but it is not for lack of research on the topic. The results of studies are often ambiguous and contradictory. One reason is that different researchers measure the same characteristic in different ways. Also, the research samples are often too small to yield reliable results, and the participants are usually not selected in a manner that ensures accurate representation of the population. Whether the differences that do exist are influenced by biology or are the product of rearing and experience is difficult to determine. In a 1983 study, parents who claimed equality as a childrearing value verbalized differently and played differently with a child dressed as a girl than when the same child was dressed as a boy (Culp, Cook, & Housley, 1983). Differential rearing, of course, could account for marked differences in behavior, temperament, and self-expectations. According to a recent meta-analysis, however, beginning around 1990, parents have shifted from a pattern of autonomy-supportive rearing strategies with boys and controlling strategies with girls to granting somewhat more autonomy and support to girls than boys (Endendijk, Groeneveld, Bakermans-Kranenburg, & Mesman, 2016).

Some Demonstrated Male–Female Differences

Back in 1974, Eleanor Maccoby and Carol Jacklin reviewed more than 2,000 studies and concluded that the evidence firmly supported three differences in cognitive performance and one difference in social behavior: (1) Girls have greater verbal ability than boys, (2) boys excel in visual-spatial ability, (3) boys excel in mathematical ability, and (4) boys exhibit more aggression than girls. Later research has supported these differences to some extent but with qualifications. First, males and females differ only on average, with considerable overlap between the groups. Second, the differences are rather specific (Hirnstein, Hugdahl, & Hausmann, 2019). Females'

verbal superiority, for example, has been documented in verbal fluency, verbal memory, and reading achievement but not in all aspects of verbal ability. Male spatial performance exceeds females' most on tasks requiring mental rotation of a three-dimensional object (like the one in Figure 7.14) and less on other spatial tasks; in fact, females have the advantage in object location memory. We will see in Chapter 8 that the difference in aggression disappears when verbal as well as physical aggression is considered.

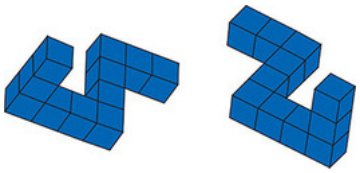


Figure 7.14 A Spatial Rotation Task.
People are presented with several pairs of drawings like these and asked whether the first could be rotated so that it looks like the second. Males are typically better at this kind of task than females. (In case you're wondering, the answer is no.)

Origins of Male–Female Differences

The best evidence that these differences are partially the result of experience is that they have decreased over the years, presumably as gender roles and expectations have changed (Hedges & Nowell, 1995; Hyde, 2014; Voyer, Voyer, & Bryden, 1995). In National Assessment of Educational Progress testing of high school seniors between 1990 and 2011, boys outnumbered girls two to one at the upper extreme of math and science achievement but had on average only a small advantage over girls (Reilly, Neumann, & Andrews, 2015). Similar trends were found in a study of 89 countries, and data suggested that progress is due to increasing gender equality (Kane & Mertz, 2012). In addition, the dramatic variation in murder rate in different countries suggests there is also a strong cultural influence on aggression; for example, the murder rate in 2019 was 105.4 per 100,000 of population in El Salvador, 5.0 in the United States, 1.0 in the United Kingdom, and 0.3 in Japan (United Nations Office on Drugs and Crime, 2019).

Although environmental influences play a significant role, gender differences in cognition and behavior also owe a great deal to biology. This is exemplified in a number of differences between male and female brains (Nguyen et al., 2019; E. S. Smith, Junger, Derntl, & Habel, 2015). Men have larger brain volumes (even after correcting for body size), and as a result, they have more gray matter and white matter than women; proportionately, however, women have more gray matter and men have more white matter. Women also have greater cortical thickness in several areas. Structural connectivity is stronger within hemispheres in men and between hemispheres in women. In addition, there are gender differences in the volume of several brain areas (Figure 7.15; Cahill, 2006), and the volume differences correspond to the density of sex hormone receptors in those areas (J. M. Goldstein et al., 2001). Most often, researchers attribute the differences to the effects of estrogens and testosterone, particularly on the organizational development of the brain during gestation. Because the effects of sex hormones on brain development are most evident in people with atypical sexual development, we will hold that discussion for the next section and focus here on activating effects occurring after birth.

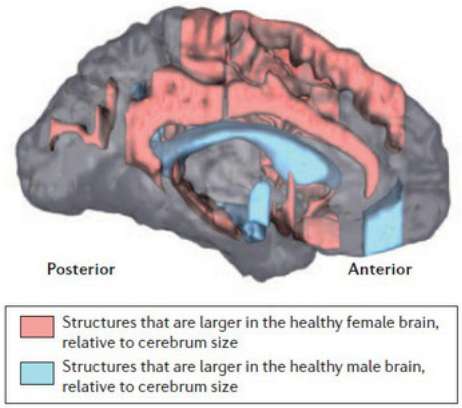


Figure 7.15 Sex Differences in Brain Volume.

Source: From "Why Sex Matters for Neuroscience," by L. Cahill, 2006, *Nature Reviews Neuroscience, 7,* p. 478. © 2006 Nature Publications. Reprinted with permission.

? How do we explain the differences in verbal and spatial abilities and in aggression?

Activational effects of the sex hormones at puberty and afterward are also important (Reilly, Neumann, & Andrews, 2017). Spatial ability is lower in men who were diagnosed with hypergonadism after puberty, and testosterone replacement in older men improves their spatial functioning (Janowsky, Oviatt, & Orwoll, 1994). Individuals identified at birth as male who take estrogens because they identify as females (transgender women) increase their scores on verbal fluency tasks, but they lose spatial performance; transgender men taking testosterone lose verbal ability but improve in spatial performance (for references, see Hulshoff Pol et al., 2006). Men kill 30 times as often as women do (Daly & Wilson, 1988), and testosterone is usually blamed for this difference. However, whether testosterone is the cause or the result of aggression is questioned because a variety of studies show, for example, that winning a sports competition increases testosterone and losing decreases it (J. Archer, 1991). The source of aggression is a complex subject, and we will deal with it more thoroughly in Chapter 8.

Differences in brain functioning are also cited as bases for gender differences, with hemispheric lateralization receiving the most attention Males tend to process spatial information in the right hemisphere and verbal and language information in the left, while females show no hemispheric preference. This is consistent with the finding we mentioned earlier regarding greater structural connectivity between hemispheres in females and greater connectivity within hemispheres in males. However, the differences in cognitive performance are so small that they required multiple meta-analyses totaling more than 40,000 participants to affirm them with confidence, and it is not yet possible to determine whether the connectivity differences account for the cognitive differences (Hirnstein et al., 2019). Imaging studies indicate that men use parietal areas to perform spatial rotations, and their scores are correlated with the amount of cortical surface in the parietal lobes. Women, on the other hand, rely more on frontal areas, suggesting that they use a different approach to solve the problem, most likely involving internal verbalization (Andreano & Cahill, 2009; Koscik, O'Leary, Moser, Andreasen, & Nopoulos, 2009). Similarly, a spatial memory task activated the right hippocampus in men, whereas women relied on the left hippocampus and reported using a verbal strategy (Frings et al., 2006; Persson et al., 2013). There are also several other indications that male and female brains work differently. Males and females have different patterns of brain activation during learning (Andreano & Cahill, 2009), pain (Naliboff et al., 2003), and stress (J. Wang et al., 2007). Males are genetically more resistant to pain, and males and females respond differently to different pain medications (J. Bradbury, 2003). Men are less affected by stress (Matud, 2004), but as you will see in subsequent chapters, males are more susceptible to autism, Tourette syndrome, and attention-deficit/hyperactivity disorder,

whereas women are more likely to suffer from depression and Alzheimer's disease. Research described in A Further Look suggests that some of these differences may be due to male–female differences in expression of their genes.

A Further Look:

GTEx Project Provides New Insight Into the Differences Between the Sexes

In the years since completion of the Human Genome Project, researchers have focused on understanding how differences in *gene expression*, genes' ability to create proteins, can provide insight into typical versus atypical human functioning. The Genotype-Tissue Expression (GTEx) Project, which began in 2010, aims to identify differences in gene expression in tissues and organs that have been donated from hundreds of different people, with the hope of better understanding diseases (National Human Genome Research Institute, 2016). Researchers at the Weizmann Institute of Science have recently used some of the GTEx data to determine why human males and females differ in disease risk, behavior, and body type in spite of sharing most genes (Gershoni & Pietrokovski, 2017). Of the approximately 20,000 genes that they examined, the researchers identified more than 6,500 that were expressed differently in males and females in at least one tissue. Sex-based gene expression differences were found not just in the reproductive organs and mammary glands but also in the heart, the skin, the liver, and the brain. These differences in gene expression likely relate to sex differences not only in fat storage, body hair, and milk production and release but also in medical issues such as drug responsiveness, heart muscle disease, and risk for Parkinson's disease. Of particular interest, there were more mutations in male-specific genes than female-specific genes, suggesting that natural selection acts less strongly on males than females, possibly because males can create many more offspring in a lifetime (due to both the Coolidge effect and gestation time).

The value of studying these differences is not to determine whether one sex is smarter or more aggressive or healthier than the other but to understand what contributes to the characteristics in either sex. An understanding of their origins could help us enhance intellectual development, reduce violence, and cure or manage diseases. From a scientific perspective, that knowledge also helps us understand how the brain develops, an issue that we will continue to pursue in the next two sections.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- What are the origins of male–female differences in verbal and spatial abilities?
- What are the arguments for environmental origins and for biological origins of male–female differences in cognitive abilities and behaviors?

BIOLOGICAL ORIGINS OF GENDER IDENTITY

For decades, sex researchers have argued about what shapes an individual's gender identity, with some believing it is formed in the first few years of life by a combination of rearing practices and genital appearance (Money & Ehrhardt, 1972) and others claiming that chromosomes and hormones are more important (M. Diamond, 1965). Our earlier discussion of the effects of XY and XX chromosomes was the simple version of the sex-determination story; in reality, development sometimes takes an unexpected turn. As you will soon see, the results not only challenge our definition of what is male and what is female but also tell us a great deal about the influence of biology on gender.

Transgender

Not everyone is comfortable with the sex assigned to them at birth. An individual may adopt a gender identity anywhere between male and female or reject gender entirely; most of the research has focused on individuals whose identity is with the other sex, so we will limit our discussion accordingly. Individuals whose gender identity does not match the sex they were assigned at birth are referred to as **transgender** or **transsexual**. They may adopt clothing and hairstyles typical of their preferred sex, take hormones to feminize or masculinize their bodies, or undergo sex-reassignment (gender-affirming) surgery. That surgery is extensive, involving removal of the testes or ovaries and remodeling of the genitals, either by removing the penis and creating a vagina or closing the vaginal opening and fashioning a penis and scrotum. It is estimated that 0.6% of U.S. adults have taken some steps to transition to the other sex (Flores, 2016). We will refer to them as male-to-female transsexual (or transgendered, MtF) or female-to-male transsexual (or transgendered, FtM). Those whose gender identity matches their birth sex will be referred to as cis-male or cis-female in this discussion.

We will use the term **gender dysphoria** to refer to the significant and persistent distress that some people feel because their sex does not match their gender identity. (Some writers use this term to refer to transgender individuals who have not opted for gender-affirming hormone therapy or surgery.) The best therapeutic outcomes have resulted not from “corrective” psychotherapy but from the requested hormonal and surgical treatment, along with supportive counseling (Saraswat, Weinand, & Safer, 2015). Gender dysphoria is estimated to occur in 0.005% to 0.014% of adult males and in 0.002% to 0.003% of adult females (American Psychiatric Association, 2013).

Gender dissatisfaction can appear as early as 3 or 4 years of age and can be due to a combination of biological and environmental influences (S. M. Burke, Cohen-Kettenis, Veltman, Klink, & Bakker, 2014; Knafo, Iervolino, & Plomin, 2005). There have been few attempts to determine what the environmental influences are, but two studies implicated childhood maltreatment (Saleem & Rizvi, 2017) and anti-androgenic pollutants (such as phthalates, found in many consumer products; Percy et al., 2016) as possibilities. Heritability of gender identity averaged 31% across a number of twin studies (Polderman et al., 2018). Gene studies have linked FtM transsexualism to alleles of the *ESR1* estrogen receptor gene and to the *CYP17* gene, which affects levels of two estrogens (estradiol and progesterone) and testosterone (Bentz et al., 2008; Cortés-Cortés et al., 2017; Foreman et al., 2019). Studies of MtF transgendered individuals have identified a handful of alleles, including variations of the *AR* androgen receptor gene and the *ERβ* estrogen receptor gene (Foreman et al., 2019; Hare et al., 2009). The authors suggested that these gene variants lead to masculinization in the brains of FtM transsexuals and undermasculinization and/or feminization of MtF transgendered brains. Two other studies using more stringent statistical tests were unable to confirm these gene associations (Fernández et al., 2014; Ujike et al., 2009).

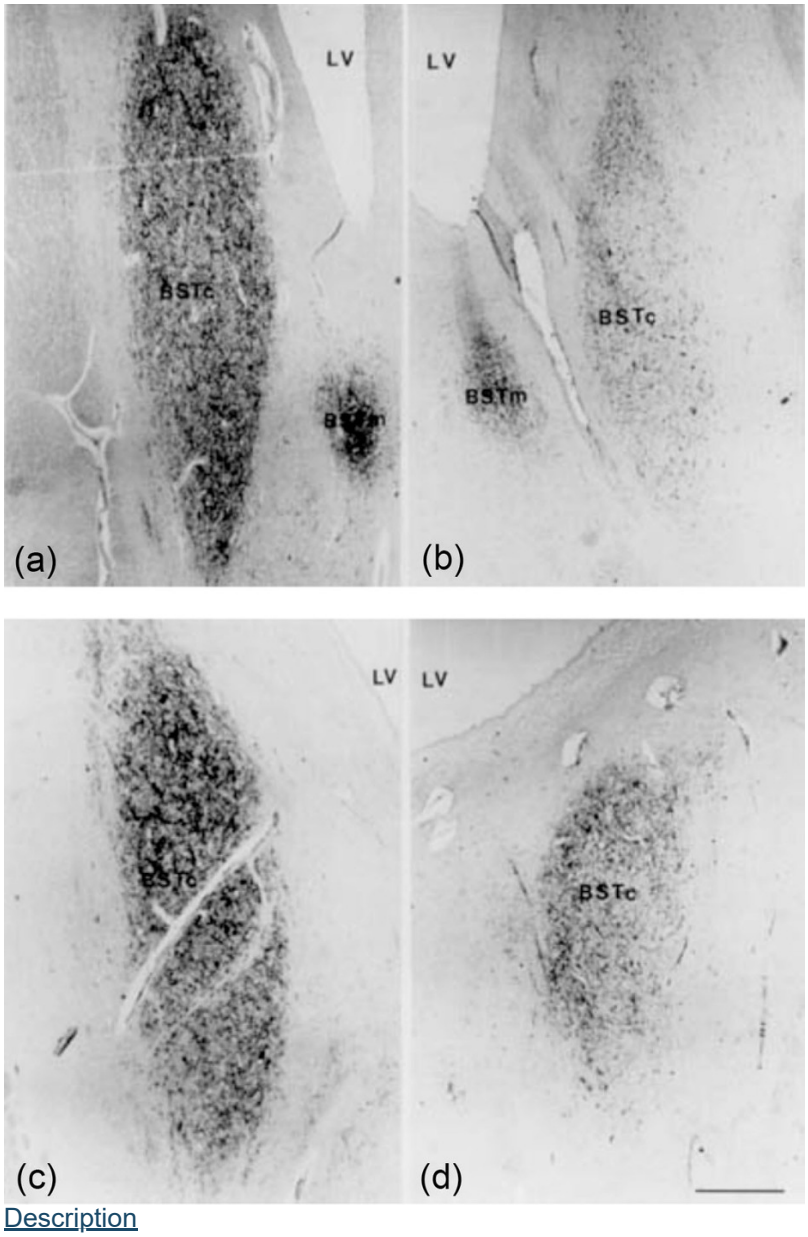
? What influences affect gender identity and gender-related behavior?

Transgender and the Brain

Several studies suggest that the brains of transgender individuals have followed a different developmental path, with various brain structures more like those of their identified sex than of their birth sex (reviewed in Saraswat et al., 2015). For example, increased cortical thickness has been reported in MtF individuals, and the brain weight of transgender individuals seems to lie in between that of cis-males and cis-females. Similarly, in MtF transsexuals, the strength of structural connectivity in four white matter tracts involved in higher cognitive functions fell halfway between that of cis-males and cis-females. These results suggest incomplete masculinization or feminization in the transsexual brain. It is possible for the development of the genitals and the brain to come under different influences because the genitals develop during the first trimester and the brain continues development throughout pregnancy and

beyond (Bao & Swaab, 2011). We will see more evidence of this in the following discussions.

The **third interstitial nucleus of the anterior hypothalamus (INAH3)** is larger in men than in women and is thought to be the human counterpart of the SDN. The **central subdivision of the bed nucleus of the stria terminalis (BSTc)** is also larger in males than in females; it is closely connected to the amygdala, hippocampus, and prefrontal cortex, and in rats it mediates pheromone signaling (E. S. Smith et al., 2015). Both have been reported to be cis-female-sized in MtF transgender individuals (Figure 7.16; Garcia-Falgueras & Swaab, 2008; Kruijver et al., 2000; J. N. Zhou, Hofman, Gooren, & Swaab, 1995). Size in FtM transsexuals was closer to cis-male size, but only two individuals were available for study. The differences appeared to be unrelated to hormone treatment or sexual orientation.



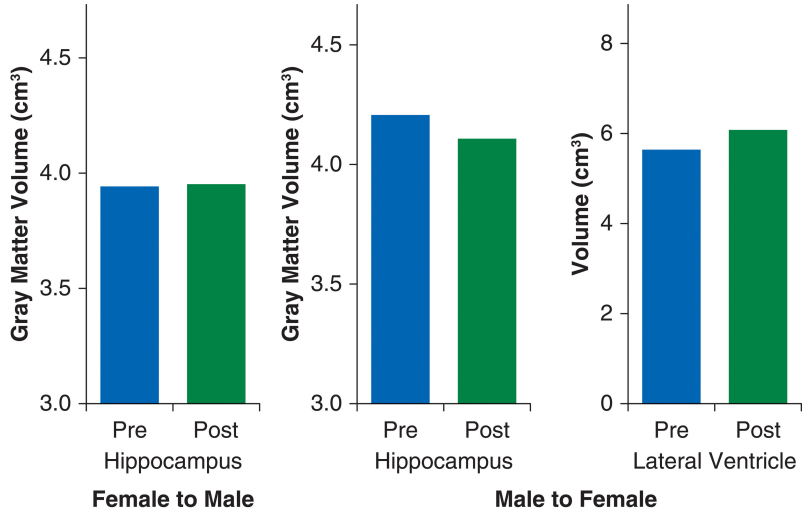
Description

Figure 7.16 BSTc Size in Male-to-Female Transgender Individuals. Representative images of the stained BSTc in a (a) heterosexual male, (b) heterosexual female, (c) gay male, and (d) male-to-female transgender individual.

Source: Figure 2, "A Sex Difference in the Human Brain and Its Relation to Transsexuality," by J.-N. Zhou, M. A. Hofman, L. J. Gooren, and D. F. Swaab, 1995, *Nature*, 378, pp. 68–70. Reprinted by permission of *Nature*, copyright 1995.

To the extent that these brain differences are reliable, we might expect to find task-based behavioral differences as well, and some have been reported. For example, when viewing an erotic video, cis-males showed increased activation in the thalamus, amygdala, orbitofrontal cortex, and insular cortex, while cis-females showed no specific pattern of activation; MtF transsexuals responded like the cis-females (Gizewski et al., 2009). And although we have cautioned about interpreting human pheromone studies, we should note that MtFs have been reported to respond to the presumed pheromone AND but not to EST (H. Berglund, Lindström, Dhejne-Helmy, & Savic, 2008). In a later study, adolescent boys and girls with gender dysphoria both responded to AND like their preferred sex. Interestingly, these preferred-sex responses showed up only in children past puberty (S. M. Burke, Cohen-Kettenis, Veltman, Klink, & Bakker, 2014). Results of similar studies have been inconsistent, though, and this lack of confirmation suggests a need for caution in interpreting the results.

While most of the studies conclude that brain structure and function are more in line with gender identity than with natal sex, about one quarter of the literature indicates the opposite (Nguyen et al., 2019). There are several possible reasons for these contrary findings. Often the number of participants in the studies has been small; unless the effect being investigated is large, the results can easily vary from one study to the next. A second problem involves the "data-snooping" issue we described in Chapter 4; scanning the entire brain and looking for any difference without doing a statistical correction for the number of comparisons makes it highly likely that one or more comparisons will be erroneously identified as different solely by chance. These two issues combined contribute to the fact that different studies often identify different brain areas. Finally, there are two potential sources of contamination: failure to control for sexual orientation, which could account for brain alterations, and including individuals who were undergoing hormone therapy. We know from studies that compared transgendered individuals before and after hormone treatment that sex hormones can modify structure and functioning in the adult brain. For example, although testosterone had no effect on the hippocampus in FtM transsexuals, estradiol and anti-androgen treatment of MtF transsexuals reduced hippocampal gray matter volume toward female values (Figure 7.17; Seiger et al., 2016). The decrease was small, but there was enough gray matter loss that it was reflected in an increase in ventricular volume.



Description

Figure 7.17 Effect of Cross-Sex Hormone Therapy on Hippocampal Volume in Transsexuals.
Testosterone treatment had no effect on FtM hippocampal volume, but estradiol and

anti-androgen treatment in MtFs resulted in decreased hippocampal volume and an associated increase in lateral ventricle volume.

Source: Adapted from Figures 2 and 3, "Subcortical Gray Matter Changes in Transgender Subjects After Long-Term Cross-Sex Hormone Administration," by R. Seiger et al., 2016, pp. 371–379. Reprinted by permission of Elsevier, copyright 2016.

The findings are strong enough to encourage further investigations, but it is difficult to reach the firm conclusions about hormonal sexualization of the brain that are suggested by animal studies. The sexual variations described in the sections that follow serve as "natural experiments" that provide valuable, and sometimes dramatic, additional information.

46,XY Intersex

At puberty, Jan failed to develop breasts or to menstruate; instead, her voice deepened, and her body became muscular, while her clitoris grew to a length of 4 centimeters (1.5 inches) and the labia partially closed over her vagina, giving the appearance of a male scrotum. Once comfortable with her tomboyishness, she was now embarrassed by her appearance and increasingly masculine mannerisms; she withdrew from peers, and her school performance began to suffer. To everyone's surprise, her doctor discovered two undescended testes in her abdomen and no ovaries. After a psychiatric evaluation, Jan's parents and doctors offered her the opportunity to change to a male sexual identity. She immediately went home and changed into boy's clothing and got a boy's haircut. The family moved to another neighborhood where they were unknown. At the new high school, Jack became an athlete, excelled as a student, was well accepted socially, and began dating girls. Surgeons finished closing the labia and moved the testes into the newly formed scrotum. Jack developed into a muscular, 6-foot-tall male with a deep voice and a heavy beard. At the age of 25, he married, and he and his wife reported a mutually satisfactory sexual relationship (Imperato-McGinley, Peterson, Stoller, & Goodwin, 1979).

Today Jack would be diagnosed as **46,XY intersex**, in which an individual has an X and a Y chromosome in each cell but, due to incomplete masculinization, has ambiguous or female external genitalia. (Medical terminology uses the term *46,XY disorder in development*, but in deference to those who contend that sexual development is a continuum, we have chosen to use the term *intersex*.) Among all the individuals identified as female at birth in Denmark between 1951 and 2000, the prevalence of 46,XY intersex was 6.4 per 100,000 (A. Berglund et al., 2016). There are several forms of 46,XY intersex, with a variety of causes relating to testosterone production or functioning. Mutations or deletions involving the *SRY* gene account for 15% of cases (Veitia et al., 1997); environmental influences include use of synthetic progesterone during gestation and, possibly, environmental contaminants, such as pesticides and herbicides that have estrogenic effects (Mendonca, Domenice, Arnhold, & Costa, 2009). The reason for Jack's unusual development was a deficiency in an enzyme (17α-hydroxysteroid) that converts testosterone into dihydrotestosterone, which masculinizes the external genitalia before birth. The large surge of testosterone at puberty enabled his body partially to carry out that process.

A deficiency in another enzyme, 5α-reductase, also reduces dihydrotestosterone levels and delays genital development. Chromosomal males are born with female-appearing or ambiguous external genitals, which then are completely virilized (masculinized) at puberty. This deficiency is genetic and is most likely to occur when there is frequent intermarriage among relatives. Of 18 such individuals in the Dominican Republic who were reared unambiguously as girls, all but one made the transition to a male gender identity after puberty, and 15 were living or had lived with women (Imperato-McGinley, Peterson, Gautier, & Sturla, 1979). The men said they realized they were different from girls and began questioning their sex between the ages of 7 and 12. Although their transition argues for the influence of genes and hormones on gender identity, such a conclusion must be tentative because the individuals had a great deal to gain from the switch in a society that puts a high premium on maleness (Cohen-Kettenis, 2005).

Eden Atwood (Figure 7.18) is a widely acclaimed jazz singer. She has recorded and performed all over the world and with the biggest names in jazz. Ms. Atwood is also remarkable for having been born with XY chromosomes and two testes. Her **androgen insensitivity syndrome**, a form of 46,XY intersex, is caused by a genetic absence of androgen receptors, which results in insensitivity to androgen. Androgen insensitivity syndrome accounts for almost two thirds of instances of 46,XY intersex (A. Berglund et al., 2016). Müllerian inhibiting hormone suppresses development of most of the female internal organs. In the partial form, a minimal sensitivity to androgens can lead to external genitals that look typically female or typically male or have characteristics of both. The individual may be reared successfully as a male or as a female. In the complete form, the individual is totally unaffected by androgens; the testes do not descend, the external genitals are feminine with a shallow vagina, and the person adopts a female identity. The condition may not be recognized until menstruation fails to occur at puberty or when unsuccessful attempts to become pregnant lead to a more complete medical examination. In the absence of testosterone's influence, androgen-insensitive individuals tend to have well-developed breasts and a flawless complexion. Because these characteristics are often combined with long, slender legs, people with androgen insensitivity syndrome repeatedly show up among female fashion models (J. Diamond, 1992).

Figure 7.18 Eden Atwood.

Source: Photo courtesy of Terry Cyr. Used with permission of Eden Atwood. ZUMA Press, Inc. / Alamy

46,XX Intersex

A person with **46,XX intersex** is partially masculinized by excess androgens or hormone treatment during gestation, resulting in more or less masculinized external genitalia. In 80% to 90% of cases, during chromosome division, the father's SRY gene crosses over from the Y to the X chromosome; when this SRY-positive X chromosome combines with the mother's X chromosome, the result is an XX individual with male characteristics. The individual develops a penis, typically normal in size, and usually comes to medical attention only as a result of infertility (Terribile et al., 2019).

Another cause of 46,XX intersex, **congenital adrenal hyperplasia (CAH)**, results from genetic mutations in genes that code for enzymes that cause the individual's adrenal glands to produce large amounts of androgens during fetal development and afterward (Figure 7.19). The internal organs are female, because no Müllerian inhibiting hormone is released, but the clitoris is enlarged and the outer labia may close to form the appearance of a scrotum, to the extent that it can be difficult to determine sex by observation alone. Postnatal hormone levels can be normalized by administering corticosteroids, and the parents often choose reconstructive surgery to reduce the size of the clitoris and eliminate labial fusion. If masculinization is more pronounced, the parents may decide to rear the child as a boy; in that case, the surgeons usually finish closing the labia and insert artificial testes in the scrotum to enhance the masculine appearance. The most common cause of CAH, 21-hydroxylase deficiency, affects 1 in every 10,000 to 20,000 births and accounts for 95% of all occurrences. Fortunately, it can be detected in the womb and treated with a synthetic corticosteroid to reduce genital ambiguity (Nimkarn & New, 2010; Therrell, 2001).

Figure 7.19 Female Infant With Congenital Adrenal Hyperplasia.
Parents of children with ambiguous genitalia often have difficulty knowing whether to rear them as boys or as girls. (The unusual pigmentation of the skin is due to excess excretion of sodium, or *salt wasting*, which often occurs with CAH.)

Source: Used with permission of Thomas A. Wilson, MD, The School of Medicine at Stony Brook University Medical Center.

It would be easy to get caught up in the unusual physical characteristics of these individuals and to be distracted from our question: What makes a person male or female? This question is the topic of A Further Look, as well as the next few pages.

A Further Look:

Sex, Gender, and Sports

Cameron Spencer/Getty Images Sport/Getty Images

When Caster Semenya of South Africa won the gold medal in the 800-meter race at the 2009 World Championships in Athletics, her strong performance and masculine physique aroused suspicions about her gender. Fueled by years of media reports that some female competitors might actually be men, the International Association of Athletics Federations (IAAF) and the International Olympic Committee (IOC) had introduced routine gender testing in the 1960s (Simpson et al., 1993). However, physical examination was soon rejected as unacceptable to many women, and chromosome testing turned out to be inadequate as a measure of performance advantage. For example, Barr body analysis, which identifies cells with XX chromosomes, rejects androgen-insensitive XY individuals, even though they receive no benefit from testosterone, but it would pass XXY males, who do benefit. The IOC and the IAAF ended routine testing in the 1990s, though both reserved the authority to request gender identification on an individual basis.

Semenya underwent gender testing, and the IAAF cleared her to compete, although it was leaked that she had female external genitals and two undescended testes (Powers, 2010). Then in 2012, the IAAF instituted a policy that barred women from competition if their androgen level reached male levels and they were responsive to androgens—intentionally leaving the androgen cutoff point for determination on a case-by-case basis (Macur, 2012). This policy was suspended in 2015, when the Court of Arbitration for Sport decided that evidence demonstrating testosterone-related increased athletic performance in women was lacking (Branch, 2015). Then in 2018 the IAAF began requiring female runners like Semenya to maintain their testosterone below a specified level in order to compete in longer endurance races, in which testosterone particularly confers an advantage (IAAF Athletics, 2018). Semenya refused, and appealed the ruling. The Court of Arbitration in Sport in Switzerland upheld the IAAF regulation, stating that it was discriminatory, but that the discrimination is necessary to ensure fair competition (Court of Arbitration for Sport, 2019). Semenya was barred from defending her 800-meter title at the World

Championships (“Semenya out of World Championships…,” 2019), and the Swiss Supreme Court dismissed her appeal (Ramsay & Martin, 2020).

Semenya’s supporters argue that she shouldn’t have to reduce her testosterone when there was no complaint that Usain Bolt’s long legs give him an 18-inch longer stride than his competitors. They also point out that the IAAF amended its rule to apply only to 46,XY individuals, not to hyperandrogenized 46,XX females (saying that the latter are less able to benefit from testosterone increases). The one thing that is clear from the controversy is that society has difficulty coming to terms with sex and its variations.

Cognitive and Behavioral Effects

As mentioned earlier, reversing the sex hormone balance during prenatal development changes the brain and later behavior in nonhuman animals. Is it possible that masculinization and feminization of the developing brain account for sex differences in behavior and cognitive abilities in humans as well? If so, then we would expect the behavior and abilities of individuals who have experienced an excess or a deficit of androgen during prenatal development to be at odds with their chromosomal sex.

That is indeed the case. Androgen-insensitive 46,XY individuals are like females in that their verbal ability is higher than their spatial performance, and their spatial performance is lower than that of other males (Imperato-McGinley, Pichardo, Gautier, Voyer, & Bryden, 1991; Masica, Money, Ehrhardt, & Lewis, 1969; Strandqvist et al., 2018). And though there have been contradictory results, evidence favors increased spatial ability in CAH women (Puts, McDaniel, Jordan, & Breedlove, 2008). Androgen-insensitive 46,XY individuals also are typically feminine in behavior, have a strong childbearing urge, and are decidedly female in their sexual identity and sexual orientation (M. Hines, 1982; Money, Schwartz, & Lewis, 1984; J. M. Morris, 1953). Although 95% of CAH women reared as girls accept a female identity, they also show behavioral shifts in the masculine direction (Dessens, Slijper, & Drop, 2005). They have been reported to be tomboyish in childhood (M. Hines, 1982); to prefer boys’ toys, such as trucks and building blocks (Berenbaum, Duck, & Bryk, 2000); and to draw pictures more typical of boys, using darker colors and including mechanical objects and excluding people (Iijima, Arisaka, Minamoto, & Arai, 2001). They also more often report male-dominated occupational choices (30% vs. 13%), interest in rough sports (74% vs. 50%), and interest in motor vehicles (14% vs. 0%; Frisén et al., 2009). There is evidence that these effects are due to androgen levels before birth rather than during postnatal development (Berenbaum et al., 2000). Gay or bisexual orientation has been reported to be as high as 37% (Money et al., 1984) and at 19% in a recent larger study (Frisén et al., 2009).

? What are the behavioral implications of 46,XX and 46,XY intersex?

Some critics claim that humans are sexually neutral at birth, and they attribute the cognitive and behavioral effects we have just seen to feminine or ambiguous rearing in response to the child’s genital appearance. (You may be beginning to appreciate the deficiencies of natural experiments.) However, some of the findings are difficult to explain from a socialization perspective. For example, the anti-miscarriage drug diethylstilbestrol (DES) given to women in the 1950s and 1960s has an androgen-like effect in the brain but does not virilize the genitals, yet DES-exposed daughters reported increased lesbian fantasy and behavior (Ehrhardt et al., 1985; Meyer-Bahlburg et al., 1995). In another study, girls exposed to a similar drug and who had non-virilized genitals scored higher in aggression than their unexposed sisters (Reinisch, 1981). In addition, the fact that androgen-insensitive 46,XY individuals perform even lower on spatial tests than their unaffected sisters and female controls (Imperato-McGinley et al., 1991) can be explained by insensitivity to androgens but not by “feminine rearing.”

Ablatio Penis and Other Natural Experiments

“Neutral-at-birth” theorists claim that individuals reared in opposition to their chromosomal sex generally accept their sex of rearing and that this demonstrates that rearing has more effect on gender role behavior than chromosomes or hormones (studies reviewed in M. Diamond, 1965). Diamond, who advocates a “sexuality-at-birth” hypothesis, argues that the reason individuals with ambiguous genitals accept their assigned gender is that the sex of rearing is usually decided by whether the genital appearance is predominantly masculine or feminine, which in turn reflects the influence of prenatal hormones. According to Diamond, there was no case in the literature where an *unambiguously* male or female individual was successfully reared in opposition to the biological sex. He and others (such as Money, Devore, & Norman, 1986) have described several instances in which individuals assigned as one sex successfully shifted to their chromosomal and gonadal sex in later years, long after the assumed window for forming gender identity (the first few years of life) had closed. Failures in predicting the later gender identity of a child with ambiguous genitals has led several experts (along with the advocacy group Accord Alliance) to advocate waiting until the child can give informed consent or at least indicates a clear gender preference; others are reluctant to see the child subjected to the social difficulties that result from an ambiguous appearance.

In 1966, an 8-month-old boy became the most famous example of resistance to sexual reassignment when the surgeon using electrocautery to perform a circumcision turned the voltage too high and destroyed the boy’s penis (called *ablatio penis*). After months of consultation and agonizing, Bruce’s parents decided to let surgeons transform his genitals to feminine-appearing ones. While sounding radical even today, this has remained the recommended practice for *ablatio penis* cases. The neutral-at-birth view was widely accepted then, and the psychologist John Money counseled the parents that they could expect their son to adopt a female gender identity (M. Diamond & Sigmundson, 1997). Bruce would be renamed Brenda, and “she” would be reared as a girl. This case study had two characteristics lacking in other “natural experiments”: The child was normal before the accident, and he happened to have an identical twin brother who served as a control.

Over the next several years, Money (1968; Money & Ehrhardt, 1972) reported that Brenda was growing up feminine, enjoying her dresses and hairdos, and choosing to help her mother in the house, while her “typical boy” brother played outside. But developmental progress was not nearly as smooth as Money claimed (M. Diamond & Sigmundson, 1997). Brenda was in fact a tomboy who played rough-and-tumble sports and fought, preferred her brother’s toys and trucks over her dolls, and even preferred to urinate in a standing position. She had private doubts about her sex beginning in the second grade, decided she was a boy at age 11, and decided to switch to living as a male at 14. Only then did Brenda’s father tell her the story of her sexual transition in infancy. Then, said Brenda, “Everything clicked. For the first time things made sense and I understood who and what I was” (p. 300).

Brenda changed her name to David and requested treatment with testosterone, removal of the breasts that had developed under estrogen treatment, and construction of a penis. The person who was isolated and teased as a girl was accepted and popular as a boy, and he attracted girlfriends. At age 25, he married Jane and adopted her three children. Although he was limited in his sexual performance, he and Jane engaged in sexual play and occasional intercourse.

But life was still not ideal. He brooded about his childhood and was often angry or depressed; after 14 years, Jane told him they should separate for a while. Troubled by his past and his present, and perhaps a victim of heredity—his mother had attempted suicide, his father became an alcoholic, and his twin brother died of an overdose of antidepressants—one spring day in 2004, David Reimer took his own life (Figure 7.20; Colapinto, 2004).

Figure 7.20 David Reimer, 1965–2004.

Source: © STR/REUTERS/Newscom

Although only seven cases of ablatio penis have been examined in the literature, there are numerous instances of male infants born with a missing or underdeveloped penis, not involving hormonal causes. These include cloacal exstrophy (malformation of the pelvic area) and penile agenesis (absence of a penis). In 311 such individuals reared as male, all accepted that role, with only one indicating possible gender dysphoria. Of the 77 reared as females, 22% transitioned later to male, and 13% more exhibited possible gender dysphoria (Meyer-Bahlburg, 2005). In another study of individuals with cloacal exstrophy who were assigned a female gender shortly after birth, most exhibited male-like behaviors and had switched to a male persona later in life (Reiner & Gearhart, 2004).

These cases indicate that the individual's own gender choice can be very resilient to change. This is further supported by the results of gender conversion therapy; in a study of nearly 28,000 transgender adults, those who had gone through gender conversion therapy were twice as likely to have attempted suicide, and the risk quadrupled if the therapy occurred before the age of 10 (Turban, Beckwith, Reisner, & Keuroghlian, 2020). A Further Look describes a recent case that highlights the need for caution about choosing a child's gender.

A Further Look:

Who Gets to Choose a Child's Sex?

Barcroft/Barcroft Media/Getty Images

M. C. was born with ambiguous genitals and a combination of male and female internal reproductive tissues (N. Baumgartner, 2017). Shortly after, his single mother was declared unfit to raise a child, so he became a ward of the South Carolina Department of Social Services (SCDSS). His doctors recommended corrective surgery, and the SCDSS granted permission. At 16 months, doctors removed his one internal testicle, reduced his penis to the size of a typical clitoris, and shaped a vagina out of the tissue that remained; 3 months later, he was adopted.

At the age of 8, he declared himself a boy and began asking his parents when he would grow a penis. His parents, his school, his church, and his pediatrician all respected his choice and regarded him as a boy. His parents sued on the grounds that the surgery had deprived M. C. of the right to procreate, likening the surgery to forced sterilization of an individual incapable of giving consent. Four years later, the hospital settled the case, awarding M. C. $440,000 (Ghorayshi, 2017). In the same week, the Human Rights Watch issued a 160-page report condemning gender reassignment surgery in children before they are able to give consent.

M. C.'s case suggests that biology will win out. But it also reminds us that biology is not simple, and gender cannot be assessed from an inspection of the genitals or altered by changing the genitals.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- How do sexual anomalies require you to rethink the meaning of male and female?
- What reasons can you give for thinking that the brains of people with sexual anomalies have been masculinized or feminized contrary to their chromosomal sex?

SEXUAL ORIENTATION

Sex researchers spend a great deal of time trying to understand why some people are attracted to members of the same sex. Whether we know it or not, we are also asking why most people are heterosexual. The answer to that question may seem obvious, but the fact that a behavior is nearly universal and widely accepted does not

mean that it requires no explanation. Studying people who are attracted to members of their own sex may be able to tell us not only about variations in sexual orientation but also about the basis for sexual attraction in general. We must preface this section by stating the term *homosexual* is considered offensive by many; as the literature frequently uses the term, we ask your forgiveness when it appears in this chapter and will attempt to use more preferred terms whenever possible.

? Why is it difficult to measure sexual orientation rates?

It is difficult to estimate how many people are gay; the numbers vary from study to study and from one country to another, due to differences in definition and sampling methods, as well as reluctance to admit membership in a stigmatized group. In a survey of 35,000 adults in the United States, 1.6% self-identified as gay and 0.7% as bisexual (Ward, Dahlhamer, Galinsky, & Joestl, 2014). These rates appear consistent with other countries; in a review of nine large studies, gay and lesbian combined numbers ranged from 1.2% to 2.1% in Canada, Australia, the United Kingdom, and Norway (Gates, 2011). Although almost two thirds of the nonheterosexual men identified themselves as exclusively gay, only one third of nonheterosexual women did so. About 8% of the population have had at least one same-sex experience, and 11% report same-sex attraction (Gates, 2011; Twenge, Sherman, & Wells, 2016). As Ellis and Ames (1987) point out, these experiences do not make a person gay any more than occasional heterosexual activity makes a person heterosexual. About 1% of people express no interest in sex at all and are referred to as asexual (Bogaert, 2004). Interestingly, when Gallup asked Americans what percentage of the U.S. population they thought was gay or lesbian, the average answer was 23% (Newport, 2015). That response hasn't changed significantly since 2002, in spite of increasing acceptance of LGBTQIA (lesbian, gay, bisexual, transgender, queer, intersex, and asexual) individuals and access to greater information.

Research does not support the belief that gay men are necessarily feminine and lesbians are masculine; only about 44% of gay men and 54% of lesbians fit those descriptions (Bell, Weinberg, & Hammersmith, 1981). Even then, they usually identify with their biological sex, so gender role, gender identity, and sexual orientation are somewhat independent of each other and probably have different origins.

It is not clear what causes these alternative sexual dimensions, which means that we do not know how to explain heterosexuality, either. There is considerable evidence for biological influences on sexual orientation, or else the topic would not appear in this chapter. But because social influences are commonly believed to be more important, we will consider this position first.

The Social Influence Hypothesis

It has been argued that being gay arises from parental influences or is caused by early sexual experiences. Bell and his colleagues (1981) expected to confirm these influences when they studied 979 gay and 477 heterosexual men. But they found no support for frequently hypothesized environmental influences, such as a dominant mother and a weak father or seduction by an older male.

Several developmental experiences do seem to differentiate gay individuals from heterosexuals, and these have been considered evidence for a social learning hypothesis (Van Wyk & Geist, 1984). But these experiences—such as spending more time with other-sex playmates in childhood, learning to masturbate by being masturbated by a member of the same sex, and same-sex contact by age 18—can just as easily be interpreted as reflecting an early predisposition to being gay. In fact, Bell and his associates (1981) concluded that gay adulthood "is just *a continuation of the earlier homosexual feelings and behaviors from which it can be so successfully predicted*" (p. 186; emphasis in original). However, they did find more evidence for an influence of learning on bisexuality than on being exclusively gay. This suggests that there might be a biological influence that varies in degree, with experience making the final decision in the individuals with weaker predispositions for being gay.

Among gay individuals, 70% remember feeling “different” as early as 4 or 5 years of age (Bell et al., 1981; Savin-Williams, 1996). Memories of feelings are suspect, because they are easily distorted in light of today’s circumstances. Memories of behavior are somewhat more reliable, and home videos from childhood are better yet. These behavioral measures show a high rate of gender nonconformity, including mannerisms and dress typical of the other sex, a tendency to engage in activities usually preferred by the other sex, and an atypical preference for other-sex playmates and companions while growing up (Bell et al., 1981; Rieger, Linsenmeier, Gygax, & Bailey, 2008). If we are to entertain a biological hypothesis of sexual orientation, though, we must come up with some reasonable explanation for how it is formed and how it is altered. There are three biological approaches to the question: *genetic*, *hormonal*, and *neural*.

Genetic and Epigenetic Influences

Twin and family studies provide the most documented evidence for a biological basis for sexual orientation. Siblings of individuals who are gay are two to seven times more likely to be gay themselves (J. M. Bailey & Bell, 1993; J. M. Bailey & Benishay, 1993; Hamer, Hu, Magnuson, Hu, & Pattatucci, 1993). Studies in the early 1990s reported concordances of about 50% in identical twins for both men and women (J. M. Bailey & Pillard, 1991; J. M. Bailey, Pillard, Neale, & Agyei, 1993). However, when volunteers were recruited without regard to their sexual orientation, concordances for men fell to 37% in one study and 18% in another, and women’s concordances dropped to 30% and 22% (J. M. Bailey, Dunne, & Martin, 2000; Långström, Rahman, Carlström, & Lichtenstein, 2010). Presumably the earlier data suffered from volunteer bias, due to gay individuals’ greater willingness to volunteer if they had a gay sibling.

The search for genes has been frustrating, which is not surprising, considering that it is likely that hundreds or even thousands of genes with small effects are involved (Ganna et al., 2019). A particular gene variation might have a significant effect in one study and go undetected in the next. The most replicated finding has involved a stretch of DNA on the X chromosome. Dean Hamer and his associates (1993) focused their attention there because gay men have more gay relatives on the mother’s side of the family than on the father’s side, and the mother contributes only X chromosomes to her sons. They found that 64% of the pairs of gay brothers they studied shared identical genetic material at one end of the X chromosome, in the region designated as Xq28 (Figure 7.21a). The location received additional confirmation in a meta-analysis of the five studies available in 1999 (Hamer, 1999) and in three more recent studies (Mustanski et al., 2005; Sanders et al., 2015; Sanders et al., 2017). A study that did not find an association with Xq28 is of questionable relevance. The five markers (stretches of DNA) for same-sex orientation that it did identify were also associated with openness to new experiences (such as trying marijuana), and the researchers counted a single same-sex experience as nonheterosexuality, so it appears the results may tell us more about novelty seeking than about sexual orientation (Ganna et al., 2019). Besides providing further support for Xq28, the study by Sanders and his colleagues (2017) identified two genes, *SLITRK6* on chromosome 13 and *TSHR* on chromosome 14. *SLITRK6* is involved in neurodevelopment, particularly in the forebrain; *TSHR* has been associated with skewed X chromosome inactivation and Graves’ disease, both of which have been found in mothers of gay men.

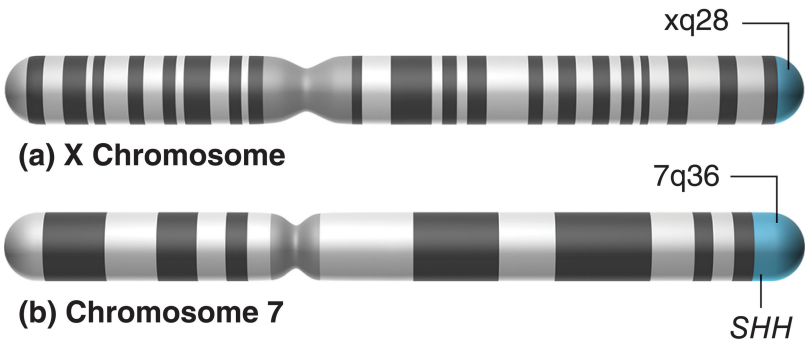


Figure 7.21 Possible Locations of Genes for Male Same-Sex Behavior. (a) The X chromosome, showing the Xq28 region. (b) Chromosome 7, indicating region 7q36 and the relative location of the *SHH* gene.

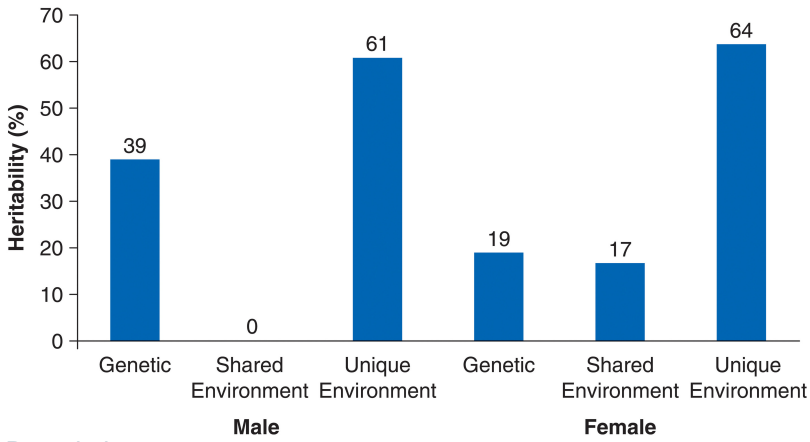
Source: Based on data from "Genetic and Environmental Effects on Same-Sex Sexual Behavior: A Population Study of Twins in Sweden," by N. Långström, Q. Rahman, E. Carlström, and P. Lichtenstein, 2010, *Archives of Sexual Behavior*, 39, pp. 75–80.

Mustanski and his colleagues (2005) also identified a stretch of DNA in the 7q36 region of chromosome 7. This association was supported by a Chinese study of gay males, which implicated a variant of the *SHH* gene located there. The *SHH* gene contributes to brain development and is involved in male–male sexual activity in fruit flies (Figure 7.21b; B. Wang et al., 2012). Female sexual orientation does not appear to be linked to Xq28 or 7q36 (S. Hu et al., 1995; Ngun & Vilain, 2014).

? What is the evidence for a biological basis for being gay?

Evidence that being gay is influenced by genes presents a Darwinian contradiction; how could non-heterosexuality survive when its genes are unlikely to be passed on by those individuals? Italian researchers have offered an intriguing proposal; the birth rate is higher in women on the mother's side of the family of gay males, so they conclude that the genes responsible also increase the women's birth rate—compensating for the gay individual's lack of productivity (Camperio Ciani, Corna, & Capiluppi, 2004; Iemmola & Camperio Ciani, 2009). A later analysis indicated that this effect is best explained by two genes, at least one of which is on the X chromosome; the researchers also suggested that the genes increase attraction to men, in both men and women (Camperio Ciani, Cermelli, & Zanzotto, 2008).

In the face of recent data indicating that environmental influences are stronger than previously thought, we need to look further for those sources. As you can see in Figure 7.22, unique environmental factors are much greater than shared (family) influences (Långström et al., 2010). At the age of 3 or 4, when pregay feelings and behaviors typically appear, there has been little opportunity for social influences outside the family to come into play. This suggests that the unique environmental influences are more likely to stem from the prenatal, biological environment rather than the later social environment. A variety of epigenetic mechanisms have been proposed as prenatal environmental factors, including skewed inactivation of X chromosomes (remember the *TSHR* gene). In females, one of each pair of X chromosomes in every cell is turned off by methylation; which of the two X chromosomes gets turned off usually varies randomly from cell to cell. However, inactivation of the same chromosome occurred in 90% of the cells in 13% of women with a gay son and 23% of the mothers of two or more gay sons, compared with only 4% of women with no gay sons (Bocklandt, Horvath, Vilain, & Hamer, 2006). Another suggestion is that an epigenetic modification of testosterone sensitivity that occurs in a parent as compensation for an atypical testosterone level could be passed on epigenetically to the offspring (W. R. Rice, Friberg, & Gavrilets, 2012). If a man with low testosterone transfers his increased sensitivity to a daughter, or a woman with high testosterone transfers her decreased sensitivity to a son, it could have significant effects on the offspring's sexual and gender development.



Description

Figure 7.22 Genetic and Environmental Contributions to Sexual Orientation.

Source: Based on data from "Genetic and Environmental Effects on Same-Sex Sexual Behavior: A Population Study of Twins in Sweden," by N. Långström, Q. Rahman, E. Carlström, and P. Lichtenstein, 2010, *Archives of Sexual Behavior*, 39, pp. 75–80.

An additional possibility for a fetal environmental influence is suggested by the fact that gay males are more likely to have older brothers (R. Blanchard, 2018). A social explanation has been ruled out because the effect is not seen if the siblings are stepbrothers, adoptive brothers, younger brothers, or sisters, but it remains if the individual is adopted out of the family. The explanation that has most often been proposed is that a Y chromosome–linked protein produces an immune reaction in the mother, which increases with each additional birth of a son. Bogaert and his colleagues (2018) have done a partial test of the hypothesis by measuring antibodies to NLGN4Y (neuroligin 4 Y-linked), a protein that plays a role in synapse development, in four groups of women. Antibody levels increased progressively from women with no sons to mothers of heterosexual sons, to mothers of gay sons with no older brothers, to mothers of gay sons with older brothers.

Prenatal Influences on Brain Structure and Function

For early researchers, the most obvious biological explanation was that same-sex orientation is due to atypical sex hormone levels. Their attempts to reverse same-sex attraction by administering testosterone to males not only were unsuccessful but often increased gay behavior (for references, see Kinsey, Pomeroy, Martin, & Gebhard, 1953). Later studies measured hormonal levels and found no evidence of either a deficit or an excess of sex hormones (Gartrell, 1982; Meyer-Bahlburg, 1984). However, by manipulating hormonal levels during gestation and shortly after birth, researchers were able to produce same-sex preference in rats, hamsters, ferrets, pigs, and zebra finches (for references, see LeVay, 1996).

? Which brain structures are different in gay males?

Critics say this effect has no bearing on human behavior, claiming that spontaneous same-sex behavior occurs in animals only when members of the other sex are unavailable and that it does not represent a shift in sexual orientation. However, about 10% of male sheep prefer other males as sex partners, and some form pair bonds in which they take turns mounting and copulating anally with each other (Perkins & Fitzgerald, 1992). A few female gulls observed on Santa Barbara Island off the coast of California form "lesbian" pairs—courting, attempting copulation, taking turns sitting on their nest, and sharing parenting if some of the eggs were fertilized during an "unfaithful" interlude with a male (Hunt & Hunt, 1977; Hunt, Newman, Warner, Wingfield, & Kaiwi, 1984). A shortage of males could be a

contributing factor, but the gulls' behavior is atypical of opportunistic same-sex behavior in that the majority of female birds stay paired for more than one season.

If sex hormones play a role in human sexual orientation, they probably do so by altering brain development during gestation. Blocking the effects of testosterone in male rats during the prenatal period and shortly after birth produced adults that preferred male company over that of an estrous female and showed lordosis and accepted mounting from the male (Swaab, Slob, Houtsmuller, Brand, & Zhou, 1995). It is difficult to measure prenatal hormone levels in humans, so researchers have looked for evidence of atypical masculinization or feminization of gay individuals' brains by examining differences known or thought to be influenced by sex hormones during development. A few differences in brain structures have been reported, including a larger right hemisphere in lesbian females and heterosexual men, with equal-sized cerebral hemispheres in gay males and straight women (Savic & Lindström, 2008). Sandra Witelson and her colleagues (2008) found a greater thickness in the part of the corpus callosum that connects spatial and language areas in gay men compared to heterosexual men; this suggests female-typical lack of lateralization and might explain the cognitive differences described shortly. In addition, the INAH3 (Figure 7.23; LeVay, 1991) and the suprachiasmatic nucleus (Swaab & Hofman, 1990) have been reported to be female-sized in gay men.

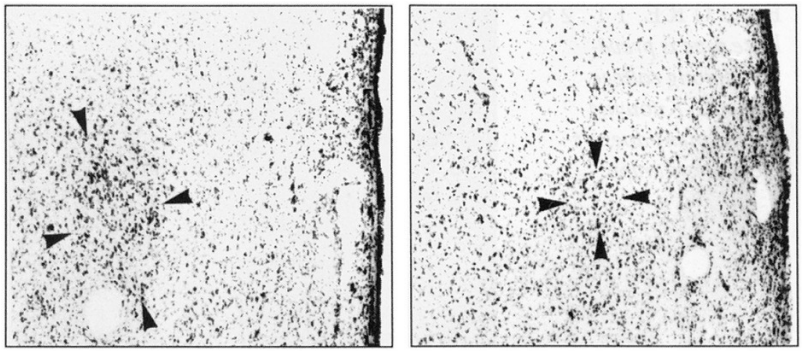
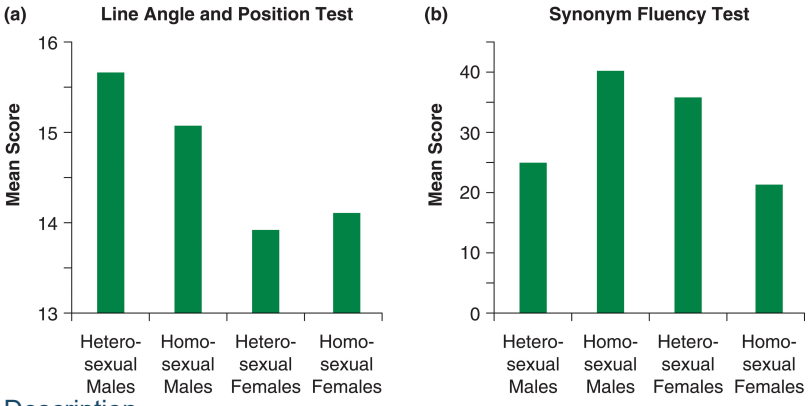


Figure 7.23 INAH3 in a Heterosexual Man (Left) and a Gay Man (Right).
The arrows indicate the boundaries of the structure. Note the smaller size in the gay man's brain.

Source: From "A Difference in Hypothalamic Structure Between Heterosexual and Homosexual Men," by S. LeVay, *Science*, *253,* pp. 1034–1047. © 1991, American Association for the Advancement of Science (AAAS). Reprinted with permission from AAAS.

From a functional perspective, a few studies have reported that gay men perform better on verbal tests and poorer on spatial tests than do heterosexual men (Figure 7.24; Collaer, Reimers, & Manning, 2007; C. M. McCormick & Witelson, 1991; Rahman, Abrahams, & Wilson, 2003). Evidence that lesbian women perform like men has been less consistent (Collaer et al., 2007; Gladue, Beatty, Larson, & Staton, 1990; Rahman et al., 2003). Some studies have reported that gay men and women respond to presumed pheromones similarly to members of the other sex (Figure 7.25; Savic et al., 2005; W. Zhou et al., 2014). Finally, relative finger length is often considered a marker of fetal androgen exposure, and the ratio of index finger to ring finger length has been reported to be male typical in lesbian women (Collaer et al., 2007; T. J. Williams et al., 2000). However, the reliability of finger ratio as a measure of prenatal androgens is controversial (Leslie, 2019).



Description

Figure 7.24 Sex-Atypical Cognitive Performance in Gay Men and Women.
(a) Spatial performance of gay men was lower than that of heterosexual men; the lesbian women's performance was slightly, but significantly, higher than that of heterosexual women. (b) Verbal fluency was higher in gay men than in all others, including heterosexual women; performance was lower for both heterosexual males and lesbian women, who did not differ significantly from each other.

Sources: (a) Based on data from "Sexual-Orientation-Related Differences in Verbal Fluency," by Q. Rahman, S. Abrahams, and G. D. Wilson, 2003, *Neuropsychology*, *17*, pp. 240–246. (b) Based on data from "Visuospatial Performance on an Internet Line Judgment Task and Potential Hormonal Markers: Sex, Sexual Orientation, and 2D:4D," by M. L. Collaer, S. Reimers, and J. T. Manning, *Archives of Sexual Behavior, 36*, pp. 177–192.

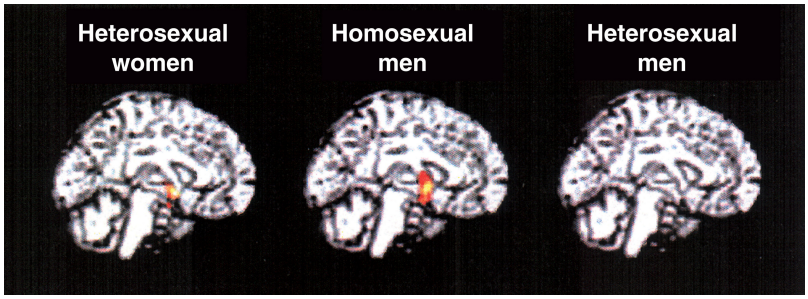


Figure 7.25 Responses of Heterosexual Women, Gay Men, and Heterosexual Men to a Presumed Male Pheromone.
Heterosexual women and gay men responded to the testosterone derivative AND in the MPOA/anterior hypothalamus, but heterosexual men did not.

Source: From "Smelling of Odorous Sex Hormone-Like Compounds Causes Sex-Differentiated Hypothalamic Activations in Humans," by I. Savic et al., *Neuron, 31,* pp. 661–668, fig. 1. © 2002.

You will notice that most of the differences relate to males; this is partly due to an unfortunate research focus on gay male behavior but also because the results have more often been negative when studying females. The latter may be because women are more often bisexual than men, which could lead to disparate results; for that reason, studies should divide nonheterosexual women into two groups. Something else you might have picked up on is that most of these studies are a decade old or older. That is not damning in itself, but it should be disturbing that most of these lines of research—on such a controversial topic—have not seen replication to date. We are faced with the dilemma of whether to draw conclusions based on either a single study or a few studies with inconsistent results or, alternatively, to suspect that later studies have yielded negative results but didn't find their way into print due to publication bias. At this point, we lack a clear idea of what forces determine human sexual orientation. What does seem likely is that the answer will turn out to be a multiplicity of factors and that much larger studies will be required to identify them.

Social Implications of the Biological Model

As is often the case, the research we have been discussing has important social implications. Some people in the gay community think that this view is not in their best interest. For them, the biological model is associated too closely with a medical "disease" explanation for their orientation. They fear that being gay will be branded as defective or even that science may find ways to identify gay predisposition in fetuses and that parents will have the "problem" corrected through genetic manipulation or abortion. Emotions are so strong among some in the LGBTQIA community that the researcher Dick Swaab was physically attacked in Amsterdam by members of the Dutch gay movement, who felt threatened by his biological studies (Swaab, 1996).

Other gay rights activists welcome the biological findings because they think that belief in biological causation will increase public acceptance of non-heterosexuality. Polls indicate they are right; in a survey of four different cultures, 56% to 85% of people who believed gay individuals are "born that way" held significantly more positive views (Ernulf, Innala, & Whitam, 1989). In the United States, acceptance of gays and lesbians has risen from 40% in 2001 to 73% in 2019, and in the past 20 years, belief that same-sex marriage should be legal has increased from 27% to 63% (Gallup, 2019). As you might expect, acceptance of non-heterosexuality increases with post–high school education (la Roi & Mandemakers, 2018).

About 75% of gay individuals themselves believe that being gay is inborn and that they have no choice (Leland & Miller, 1998). When Congressman Barney Frank of Massachusetts (Figure 7.26) was asked if he ever considered whether switching to the straight life was a possibility, he replied, "I wished it was. But it wasn't. I can't imagine that anybody believes that a 13-year-old in 1953 thinks, 'Boy, it would be really great to be a part of this minority that everybody hates and to have a really restricted life'" (Dreifus, 1996, p. 25). The nature-versus-nurture debate will not be settled to everyone's satisfaction anytime soon, but when we do understand the origins of sexual orientation, they will almost certainly include a complex mix of heredity, hormones, neural structures, and environmental effects, mostly prenatal (LeVay, 1996).

Figure 7.26 Former U.S. Congressman Barney Frank.
In 2012, Frank became the first member of Congress to marry someone of the same gender while in office.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- How has the social influence hypothesis fared in explaining non-heterosexuality?
- What is the evidence that being gay has a biological cause?
- Organize your knowledge: Make a table of the structural and functional brain differences that may distinguish gay individuals from heterosexual individuals.

Include a brief explanation and critique.

IN PERSPECTIVE

The finding that sex is not motivated by any tissue deficit caused researchers to look to the brain for its basis. What they found was a model for all drives that focused on the brain rather than on tissues that lacked nutrients or water or was too cold. This view changed the approach to biological motivation, and it meant that gender identity and gender-specific behavior and abilities might all be understood from the perspective of the brain.

The fact that a person's sexual appearance, gender identity, and behavior are sometimes in contradiction with each other or with the individual's chromosomes makes sex an elusive concept. Research is helping us understand that many differences between the sexes are cultural inventions and that these differences once thought to be a matter of choice have strong biological origins. As a result, society is slowly coming around to the idea that distinctions should not be made on the basis of a person's sex, physical appearance, or sexual orientation. These issues are emotional, as are the important questions behind them: Why are we attracted to a particular person? Why are we attracted to one individual and not another? Why do we feel male, female, or something else entirely? The emotion involved often obscures an important point: that the answers keep leading us back to the brain, which is why some have called the brain the primary sex organ.

? Why is the search for a biological basis of being gay a social issue?

Chapter Summary

Sex as a Form of Motivation

- Although there is no tissue deficit, sex involves arousal and satiation like other drives, as well as hormonal and neural control. Also like the other drives, sex can be thought of as a need of the brain.
- The key elements in human sexual behavior are testosterone and progesterone; structures in the hypothalamus; sensory stimuli, such as certain physical characteristics; and, at least in animals, pheromones.

The Biological Determination of Sex

- Differentiation as a male or a female depends on the combination of X and Y chromosomes and the presence or absence of testosterone.
- Testosterone controls the differentiation not only of the genitals and internal sex organs but also of the brain.

Gender-Related Behavioral and Cognitive Differences

- Evidence indicates that females exceed males in some verbal abilities and that males are more aggressive and score higher in visual-spatial abilities. A male advantage in mathematics appears to be limited to the upper end of performance.
- At least some of these differences appear to be partly due to differences in the brain and in hormones.
- Several structural differences have been identified in male and female brains.

Biological Origins of Gender Identity

- Transgender individuals and people with sexual variations challenge our idea of male and female.
- The cognitive abilities and altered sexual orientation of people with sexual anomalies suggest that the human brain is masculinized or feminized before birth. This view is partially supported by hormonal and brain structure studies.

Sexual Orientation

- The idea that sexual orientation is entirely learned has not fared well.
- Evidence indicates that being gay, and thus heterosexuality, is influenced by genes, epigenetic effects, prenatal hormones, and brain structure alterations, along with other factors.

- The biological view is controversial among the LGBTQIA community, but most believe that it promotes greater acceptance, and research suggests that this is the case.

Study Resources

For Further Thought

- Do you think the cognitive differences between males and females will completely disappear in time? If not, would they in an ideal society? Explain your reasons.
- Some people believe that parents should have their child's ambiguous genitals corrected early, and others think it is better to see what gender identity the child develops. What do you think, and why?
- Do you think neuroscientists have made the case yet for a biological basis for transsexualism? For being gay? Why or why not?

Test Your Understanding

1. Compare sex with other biological drives.
2. Describe the processes that make a person male or female (limit your answer to typical development).
3. Discuss sex as a continuum of gradations between male and female, rather than a male-versus-female dichotomy. Give examples to illustrate.
4. Identify any weak points in the evidence for a biological basis for non-heterosexuality (ambiguous results, gaps in information, and so on) and indicate what research needs to be done to correct the weaknesses.

Select the best answer:

1. Before undergoing her gender reassignment surgery, Caitlyn Jenner took estrogen supplements to start developing breasts and a more female-typical body shape. The changes to her body as a result of the estrogen supplements were _____ effects.
    1. activating
    2. organizing
    3. activating and organizing
    4. None of the above
2. Of the following, the best argument that sex is a drive like hunger and thirst is that
    1. almost everyone is interested in sex.
    2. sexual motivation is so strong.
    3. sexual behavior involves arousal and satiation.
    4. sexual interest varies from one time to another.
3. Pheromones
    1. synchronize menstrual cycles in women living together.
    2. contribute to aggressive behavior in animals.
    3. have a questionable role in human behavior.
    4. Both a and b
    5. Both b and c
4. A likely result of the Coolidge effect is that an individual will
    1. be monogamous.
    2. have more sex partners.
    3. prolong a sexual encounter.
    4. prefer attractive mates.
5. The part of the sexual response cycle that most resembles homeostasis is
    1. excitement.

2. the plateau phase.
3. orgasm.
4. resolution.

6. The increase in testosterone on nights that couples have intercourse is an example of
    1. an organizing effect.
    2. an activating effect.
    3. cause.
    4. effect.
7. The sex difference in the size of the sexually dimorphic nucleus in animals is due to
    1. experience after birth.
    2. genes.
    3. sex hormones.
    4. both genes and experience.
8. The most prominent structure in the sexual behavior of female rats is the
    1. MPOA.
    2. medial amygdala.
    3. ventromedial nucleus.
    4. sexually dimorphic nucleus.
9. The chromosomal sex of a fetus is determined
    1. by the sperm.
    2. by the egg.
    3. by a combination of effects from the two.
    4. in an unpredictable manner.
10. The main point of the discussion of cognitive and behavioral differences between the sexes was to
    1. illustrate the importance of experience.
    2. make a case for masculinization and feminization of the brain.
    3. make the point that men and women are suited for different roles.
    4. explain why men usually are dominant over women.
11. Evidence suggests that transsexualism is due to
    1. genes.
    2. early treatment by parents.
    3. hormones.
    4. an immune response in the mother.
12. The term that describes a person with XX chromosomes and masculine genitals is
    1. gay.
    2. ablatio penis.
    3. androgen-insensitive male.
    4. 46,XX intersex.
13. The best evidence that the *brains* of people with sexual variations have been masculinized or feminized contrary to their chromosomal sex is/are their
    1. behavior and cognitive abilities.
    2. genital appearance.
    3. physical appearance.
    4. adult hormone levels.
14. Testosterone injections in a gay man would most likely
    1. have no effect.
    2. increase his sexual activity.
    3. make him temporarily bisexual.
    4. reverse his sexual orientation briefly.
15. Evidence that lesbianism has a biological origin is
    1. that there is a high concordance among identical twins.
    2. weaker than it is for gay males.
    3. that a brain structure is larger in lesbians and men than in heterosexual women.
    4. Both a and b
    5. Both b and c
16. Environmental influences on sexual orientation are
    1. insignificant in size.
    2. mostly from peers.
    3. mostly within the family.

4. most likely prenatal.

Answers:

1. a, 2. c, 3. e, 4. b, 5. d, 6. d, 7. c, 8. c, 9. a, 10. b, 11. c, 12. d, 13. a, 14. b, 15. b, 16. d.

For Further Reading

1. *Why Is Sex Fun? The Evolution of Human Sexuality*, by Jared Diamond (Basic Books, 1997), takes an evolutionary approach to answer questions such as why humans have sex with no intention of procreating and why the human penis is proportionately larger than in other animals.
2. "The Pheromone Myth: Sniffing Out the Truth," by Richard Doty (*New Scientist*, February 24, 2010, 28–29), is based on the author's book *The Great Pheromone Myth* (Johns Hopkins University Press, 2010), in which he dismisses pheromones in humans as nothing more than learned odor preferences or, in some cases, the result of bad research.
3. *Sex Differences in Cognitive Abilities*, by Diane Halpern (4th ed., Psychology Press, 2011), describes research on cognitive differences and attempts to separate well-reasoned, data-supported conclusions from politicized pseudoscience.
4. *Brain Storm: The Flaws in the Science of Sex Differences*, by Rebecca M. Jordan-Young (Harvard University Press, 2011), criticizes studies of sex-related brain differences, claiming they fail to meet the standards of scientific research.
5. *Our Sexuality*, by Robert Crooks, Karla Baur, and Laura Widman (14th ed., Cengage, 2021), has become a classic textbook in the field, covering anatomy and physiology, gender issues, orientation, sexual difficulties, and more.
6. "Why Sex Is Not Binary," by Anne Fausto-Sterling (*New York Times*, October 25, 2018, https://www.nytimes.com/2018/10/25/opinion/sex-biology-binary.html), argues for a more complex view of sex and decries current efforts of the U.S. Department of Health and Human Services to define sex as male or female as determined at birth.
7. *As Nature Made Him: The Boy Who Was Raised as a Girl*, by John Colapinto (HarperCollins, 2000), tells the story of David Reimer. The book is described by reviewers as "riveting," with a touching description of Reimer's suffering and of his parents' and brother's support of him.
8. *Making Sense of Intersex: Changing Ethical Perspectives in Biomedicine*, by Ellen Feder (Indiana University Press, 2014), makes the argument that decisions about the treatment of children with intersex conditions should be the collective responsibility of the children, their parents, and their doctors.
9. "The Transsexual Brain—A Review of Findings on the Neural Basis of Transsexualism" (*Neuroscience and Biobehavioral Reviews*, 2015, *59,* 251–266), is a comprehensive review of literature in the field.

Key Terms

activating effects 215

androgen insensitivity syndrome 224

androgens 204

castration 204

central subdivision of the bed nucleus of the stria terminalis (BSTc) 221

congenital adrenal hyperplasia (CAH) 224

Coolidge effect 204

dihydrotestosterone 215

estrogens 204

estrus 205

46,XX intersex 224

46,XY intersex 223

gender 213

gender dysphoria 221

gender identity 213

gender role 213

gonads 214

hypogonadism 205

medial amygdala 207

medial preoptic area (MPOA) 206

Müllerian ducts 214

Müllerian inhibiting hormone 215

organizing effects 215

ovaries 214

oxytocin 204

pheromones 211

progesterone 204

sex 213

sexually dimorphic nucleus (SDN) 207

testes 215

testosterone 204

third interstitial nucleus of the anterior hypothalamus (INAH3) 221

transgender 220

transsexual 220

ventromedial hypothalamus (VMH) 207

vomeronasal organ (VNO) 211

Wolffian ducts 215

Descriptions of Images and Figures

Back to Figure

The phases in the sexual response cycle of males are excitement, plateau, orgasm, refractory period, and resolution. Sometimes, an orgasm and another refractory

period occur before resolution.

The phases in the sexual response cycle of females are excitement, plateau, two orgasms, and resolution.
Back to Figure

The horizonal axis is labeled days before menstruation, and ranges from negative 18 to 0 in unit increments. The vertical axis is labeled female-initiated heterosexual activities in mean number per day, and ranges from 0 to 0.4, in increments of 0.1. The estimated time of ovulation is between negative 15 and negative 13 days. The approximate data from the graph are tabulated below.

Back to Figure

The horizontal axis is labeled time of evening and lists early and late. The vertical axis is labeled testosterone in logarithmic units, and ranges from 0.0 to 1.0 in increments of 0.1. The approximate data from the graph are tabulated below.

Back to Figure

The horizontal axis list amygdala condition. The vertical axis is labeled investigation time, and ranges from 0 to 100 in increments of 25. The approximate data from the graph are tabulated below.

Back to Figure

The images show an opening labeled V, a region labeled A C, and S D N-P O A.

1. In an adult male, S D N-P O A is dark and of a large size, and O C is located inferior to it.
2. In an adult female, S D N-P O A is lighter and smaller, and S C N is located inferior to it. V is narrower in an adult female than in an adult male.
3. In an adult female exposed to testosterone, S D N-P O A is dark and of a large size. V is narrower in an adult female exposed to testosterone than in an adult male. O C is located inferior to V. In an adult female exposed to diethylstilbestrol, S D N-P O A is light and of a large size. V is closed and O C is located inferior to V.

Back to Figure

The horizontal axis is labeled sample number, and ranges from 1 to 17 in unit increments. Baseline is at sample number 1. Female 1 is present between sample numbers 2 and 12 and female 2 is present between sample numbers 13 and 17. A clear screen separating male from female is at samples 2, 11, and 13. The left vertical axis is labeled Dopamine concentration in percent baseline and ranges from 0 to 200. The approximate data from the graph are tabulated below.

The right vertical axis is labeled vaginal penetration frequency, and ranges from 0 to 15 in increments of 5. The approximate data from the graph are tabulated below.

Back to Figure

The two types of aggression are antagonistic aggression and protective aggression. The two types of intimacy are sexual intimacy and nurturant intimacy. The effects of aggression and intimacy on the hormones and the effect of hormones on social bonding are as follows.

- Vasopressin: Antagonistic aggression has a negative effect on vasopressin and protective aggression has a positive effect on it. Vasopressin has a positive effect on social bonding.
- Testosterone: Antagonistic aggression, protective aggression, and sexual intimacy have a positive effect on testosterone and nurturant intimacy has a

negative effect on it. Testosterone has negative effect on social bonding.

- Oxytocin: Sexual intimacy and nurturant intimacy has positive effect on oxytocin, which in turn has a positive effect on social bonding.

Back to Figure

The illustration shows the olfactory mucosa located superior to the nasal cavity, which in turn is located superior to the vomeronasal organ. A magnified view of the olfactory mucosa shows axons from one end of the olfactory receptor cells in the nasal cavity extending into the olfactory bulb and forming bunches of axons. Olfactory cilia or dendrites are on the other end of the olfactory receptor cells.

Back to image

The horizontal axis lists the voles. The vertical axis is labeled time in contact, and ranges from 0 to 80 in increments of 20. The approximate data from the graph are tabulated below.

Back to Figure

Before division, the female cell consists of two X chromosomes, and the male cell consists of an X chromosome and a Y chromosome. The female cell produces two eggs, each consisting of one X chromosome, and the male cell produces two sperms, one consisting of X chromosome and the other consisting of Y chromosome. The fertilized egg is female with two X chromosomes when an egg fuses with a sperm that has X chromosome, and is male with an X chromosome and a Y chromosome when an egg fuses with a sperm that has Y chromosome.

Back to Figure

The undifferentiated system consists of gonads, Wolffian duct, and Müllerian duct. In a differentiated male, the gonads develop into testes and the Wolffian duct develops into vas deferens. The other organs in the differentiated male are seminal vesicle leading to ejaculatory duct, prostate, and urethra passing through the penis. In a differentiated female, the gonads develop into ovaries, and the Müllerian duct develops into Fallopian tube. The differentiated female consists of a uterus that leads to cervix, vagina, urethra, and vaginal opening.

Back to Figure

1. Embryo, 6 weeks: The genital consists of a urethral fold leading to glans area. The fold is flanked by labioscrotal swelling. The anus is located posterior to the fold and the tail that is removed is posterior to the anus.
2. Fetus, second trimester: The female genital consists of glans at the top of the urogenital slit and anus at the bottom. The male genital consists of glans at the top of the urethral slit and anus at the bottom.
3. Birth: The female genital consists of the following structures from inside to outside: Vagina, opening of urethra, inner labia, outer labia, and glans of the clitoris. The male genital consists of the following structures from top to bottom: Glans of the penis, shaft of the penis, and scrotum. Glans of the penis and clitoris, shaft of the penis, inner and outer labia, and scrotum are structures with common origins.

Back to Figure

Cholesterol forms progesterone, which forms testosterone. Testosterone produces estradiol in the presence of aromatase. All structures consist of a row of three cyclohexane and a cyclopentane fused together.

In cholesterol, the cyclohexane on the left is bonded to a hydroxyl group, the cyclohexane in the middle consists of a double bond, and the cyclopentane is bonded to the sixth carbon atom of 2-methylhexane.

In progesterone, the cyclohexane on the left consists of a double bond and is double bonded to an oxygen atom, and the cyclopentane is bonded to an aldehyde group.

In testosterone, the cyclohexane on the left consists of a double bond and is double bonded to an oxygen atom, and the cyclopentane is bonded to a hydroxyl group.

In estradiol, the cyclohexane on the left consists of three double bonds in alternating positions and is bonded to a hydroxyl group, and the cyclopentane is bonded to a hydroxyl group.
Back to Figure

The images show a stained B S T c in different individuals.

1. B S T c is tear-shaped, and it is stained dark.
2. B S T c is tear-shaped, and it is stained very light.
3. B S T c is tear-shaped, and its upper half is stained darker than the lower half. A slit appears across B S T c.
4. B S T c is shaped like an upright oval, and it is shaded light.

Back to Figure

In all graphs, the horizontal axis lists pre and post.

The first graph is titled Hippocampus, female to male. The vertical axis is labeled Gray volume matter in centimeters cubed, and ranges from 3.0 to 4.5 in increments of 0.5. The approximate data from the graph are tabulated below.

The second graph is titled Hippocampus, male to female. The vertical axis is labeled Gray volume matter in centimeters cubed, and ranges from 3.0 to 4.5 in increments of 0.5.

The third graph is titled Lateral Ventricle, male to female. The vertical axis is labeled Volume in centimeters cubed, and ranges from 0 to 8 in increments of 2.

Back to Figure

The horizontal axis lists the factors for male and female. The vertical axis is labeled Heritability in percentage, and ranges from 0 to 70, in increments of 10. The data from the graph are tabulated below.

Back to Figure

In both graphs, the horizontal axis lists individuals. Graph a is titled Line angle and position test, and the vertical axis ranges from 13 to 16 in increments of 0.5. Graph b is titled Synonym fluency test, and the vertical axis ranges from 0 to 45 in increments of 5. The approximate data from both graphs are tabulated below.

8 EMOTION AND HEALTH

Flashpop/DigitalVision/Getty Images

Emotion and the Nervous System

Autonomic and Muscular Involvement in Emotion

The Emotional Brain

A Further Look | Why Bob Doesn't Jump Out of Airplanes

Concept Check

Stress, Immunity, and Health

Stress as an Adaptive Response

A Further Look | How Puffer Fish Manage Stress

Negative Effects of Stress

A Further Look | One Aftermath of Disaster Is Stress-Related Brain Damage

Social, Personality, and Genetic Factors

Pain as an Adaptive Emotion

Concept Check

Biological Origins of Aggression

The Brain's Role in Aggression

A Further Look | A Bug That Causes Road Rage?

Hormones and Neurotransmitters in Aggression

Heredity and Environment

A Further Look | Neurocriminology, Responsibility, and the Law

Concept Check

In Perspective

Chapter Summary

Study Resources

After reading this chapter, you will be able to

8.1 Describe the brain structures and neurotransmitters involved in emotion.

8.2 Explain how the body and the peripheral nervous system contribute to the experience of emotion.

8.3 Identify the adaptive and maladaptive components of the stress response.

8.4 Discuss the contributions of genetics and environment to stress responses and the immune system.

8.5 Compare the affective and sensory components of pain.

8.6 Examine the brain structures and the transmitter and hormonal systems involved in aggression.

8.7 Understand the genetic and environmental factors influencing aggression.

When Jane was 15 months old, she was run over by a vehicle. The injuries seemed minor, and she appeared to recover fully within days of the accident. By the age of 3, however, her parents noticed that she was largely unresponsive to verbal or physical punishment. Her behavior became progressively disruptive, and by the age of 14, she had to be placed in the first of several treatment facilities. Although her intelligence was normal, she often failed to complete school assignments. She was verbally and

physically abusive to others, she stole from her family and shoplifted frequently, and she engaged in early and risky sexual behavior that resulted in pregnancy at the age of 18. She showed little if any guilt or remorse; empathy was also absent, which made her dangerously insensitive to her infant's needs. Because her behavior put her at physical and financial risk, she became entirely dependent on her family and social agencies for financial support and management of her personal affairs.

Magnetic resonance imaging (MRI) revealed that there was damage to Jane's prefrontal cortex, which is necessary for making judgments about behavior and its consequences. People who sustain damage to this area later in life show an understanding of moral and social rules in hypothetical situations, but they are unable to guide their behavior according to these rules, so they regularly make choices that lead to financial losses and the loss of friends and family relationships (Bechara, Damasio, Damasio, & Lee, 1999). People like Jane, whose injury occurred in infancy, cannot even verbalize these rules when confronted with a hypothetical situation, and their moral development never progresses beyond the motivation to avoid punishment; they not only make a mess of their own lives but also engage in behavior that harms others, such as stealing (S. W. Anderson, Bechara, Damasio, Tranel, & Damasio, 1999).

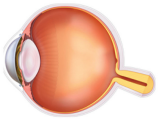
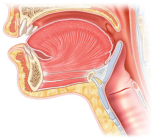
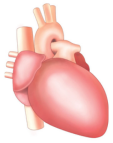
Emotion enriches our lives with, as the writer Virginia Woolf put it, its "buzzing, humming, soaring, and roaring." It also motivates our behavior: Anger intensifies our defensive behavior, fear accelerates flight, and happiness encourages the behaviors that produce it. Emotion adds emphasis to experiences as they are processed in the brain, making them more memorable (A. K. Anderson & Phelps, 2001); as a result, we are likely to repeat the behaviors that bring joy and avoid the ones that produce danger or pain. Although Jane was intelligent, her injury left her unable to learn from her emotional experiences. According to Antonio Damasio (1994), reason without emotion is inadequate for making the decisions that guide our lives and, in fact, make up our lives.

EMOTION AND THE NERVOUS SYSTEM

If asked what *emotion* means, you would probably think first of what we call "feelings"—the sense of happiness or excitement or fear or sadness. Then you might think of the facial expressions that go along with these feelings: the curled-up corners of the mouth during a smile, the knit brow and red face of anger. Next you would probably visualize the person acting out the emotion by fleeing, striking, embracing, and so on. Emotion is all these and more; a working definition might be that **emotion** is an increase or a decrease in physiological activity that is accompanied by feelings that are characteristic of the emotion and often accompanied by a characteristic behavior or facial expression. Having said that mouthful, we suspect you will understand why Joseph LeDoux (1996) wrote that we all know what emotion is until we attempt to define it. We will talk about these different facets of emotion in the following pages, along with some practical implications in the form of aggression and health.

Autonomic and Muscular Involvement in Emotion

To the neuroscientist, the most obvious component of emotional response is sympathetic nervous system activation. You may remember from Chapter 3 that the sympathetic system activates the body during arousal; it increases heart rate and respiration rate, increases sweat gland activity, shuts down digestion, and constricts the peripheral blood vessels, which raises blood pressure and diverts blood to the muscles. As you will see in the section on stress, the sympathetic system also stimulates the adrenal glands to release various hormones, particularly cortisol. At the end of arousal, the parasympathetic system puts the brakes on most bodily activity, with the exception that it activates digestion. In other words, the sympathetic nervous system prepares the body for "fight or flight"; in contrast, the parasympathetic system generally reduces activity and conserves and restores energy (Figure 8.1).

Sympathetic		Parasympathetic
	Eyes	
Pupils dilated, dry; far vision		Pupils constricted, moist; near vision
	Mouth	
Dry		Salivating
	Skin	
Goose bumps		No goose bumps
	Palms	
Sweaty		Dry
	Lungs	
Passages dilated		Passages constricted
	Heart	
Increased rate		Decreased rate
	Blood	
Supply maximum to muscles		Supply maximum to internal organs
	Adrenal glands	
Increased activity		Decreased activity
	Digestion	
Inhibited		Stimulated

Description

Figure 8.1 Comparison of Sympathetic Activity During Emotional Arousal With Parasympathetic Activity During Relaxation.

Source: Created for this book by Epicstudios, inc

? What effect does the autonomic nervous system have during emotions?

Of course, muscular activation is involved in the external expression of emotion, such as smiling or fleeing or attacking. It is also a part of the less obvious responses of emotion, such as the bodily tension that not only prepares us to act but also produces a headache and aching muscles when we try to write a paper the night before it is due. Autonomic and muscular arousal are adaptive, because they prepare the body for an emergency and help it carry out an appropriate response. They are also an important part of the emotion itself, though the exact nature of their contribution has been the subject of controversy. Fortunately, as you will see from the following discussion, competing theories are one of the engines driving research and scientific advancement.

? How do the James-Lange and cognitive theories disagree? What evidence is there for each?

The Role of Feedback From the Body

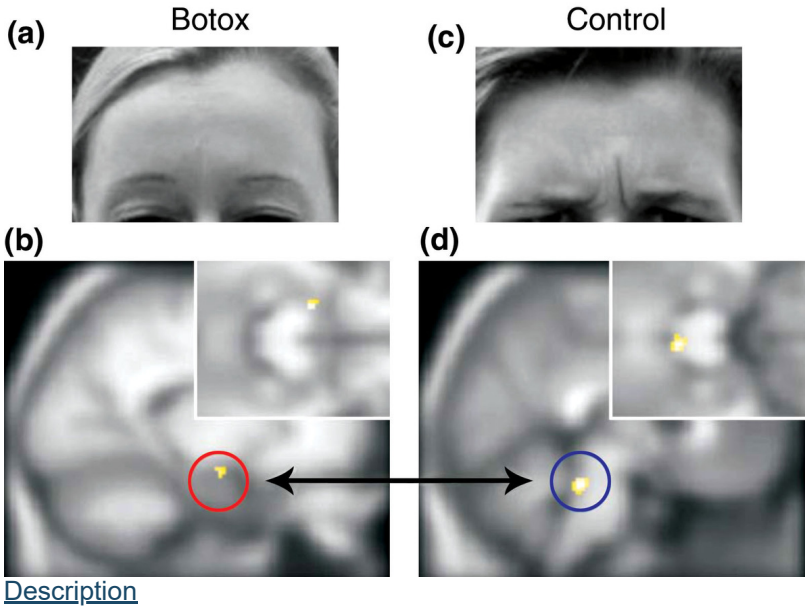
Well over a century ago, the American psychologist William James (1893) and the Danish physiologist Carl Lange (1885/2010) independently proposed what has come to be known as the **James-Lange theory**: Emotional experience results from the physiological arousal that precedes it, and different emotions are the result of different patterns of arousal. In our discussion of research ethics in Chapter 4, we talked about an experiment by Albert Ax (1953) in which participants either were made angry by an insulting experimenter or were frightened by the possibility of a dangerous electric shock. Consistent with the James-Lange theory, the two emotions were accompanied by different patterns of physiological activity. Seventy years after James and Lange, Stanley Schacter and Jerome Singer (1962) took a contrary position in their **cognitive theory**; they stated that the identity of the emotion is based on the cognitive assessment of the situation, and physiological arousal contributes only to the emotion's intensity. Their research demonstrated how easily people could misidentify emotions depending on the environmental context. For example, young men who were interviewed by an attractive woman while crossing a swaying footbridge 230 feet above a rocky river included more sexual content in brief stories they were asked to write later and were more likely to call the phone number the young woman gave them than were men who were interviewed 10 minutes after crossing the bridge (D. G. Dutton & Aron, 1974).

Studies like these have not determined that one theory is right and the other is wrong. Barlassina and Newen (2013) argue that neither is adequate; in their *integrative embodiment theory of emotions*, they maintain that bodily sensations are a critical component of emotions, but these perceptions must be integrated with cognitive information. Nevertheless, incorrect theories can be useful if they generate research, and the competition between these two has produced valuable insights into emotion. A good example is the contribution of facial expressions to emotional experience. Experimenters have had to be very inventive in doing facial expression studies; obviously, they can't just tell people to smile or frown and then ask them what emotion they're feeling. Paul Ekman and his colleagues (Levenson, Ekman, & Friesen, 1990) instructed their research participants to contract specific facial muscles to produce different expressions (Figure 8.2); for example, to produce an angry expression, they were told to pull their eyebrows down and together, raise the upper eyelid, and push the lower lip up with the lips pressed together (p. 365). The posed facial expressions for happiness, fear, anger, disgust, sadness, and surprise each resulted in the experience of the intended emotion, along with a distinct pattern of physiological arousal.

Figure 8.2 Emotional Expressions Posed Using Ekman's Instructions.

Courtesy of Paul Ekman.

Induced facial poses also influence how the person interprets the environment. Volunteers rate a stimulus as more painful when they are making a sad face than a happy or neutral one (Salomons, Coan, Hunt, Backonja, & Davidson, 2008), and college students rate *Far Side* cartoons as more amusing when they are holding a pen between the teeth, which induces a sort of smile, than when they hold the pen between the lips, producing a frown (Strack, Martin, & Stepper, 1988). More strikingly, women who have had their corrugator muscles paralyzed by injecting botulinum toxin (Botox) to remove frown lines are unable to frown, and they report less negative mood—even if they don't perceive themselves as more attractive (M. B. Lewis & Bowler, 2009). In addition, when these women attempt to imitate angry expressions, they produce less activation of the amygdala than women who have not had Botox treatment (Figure 8.3; Hennenlotter et al., 2009).



Description

Figure 8.3 Disabling Corrugator Muscle Reduces Amygdala Response to Simulated Anger.
A woman treated with Botox is unable to produce the facial expression of anger (a) and shows little activation of the amygdala (b). A control subject makes the expected facial expression (c) and produces much greater amygdala activation (d).

Source: Adapted from "The Link Between Facial Feedback and Neural Activity Within Central Circuitries of Emotion—New Insights from Botulinum Toxin-Induced Denervation of Frown Muscles," by A. Hennenlotter, et al. 2009, *Cerebral Cortex, 19*, 537-542. By permission of Oxford University Press.

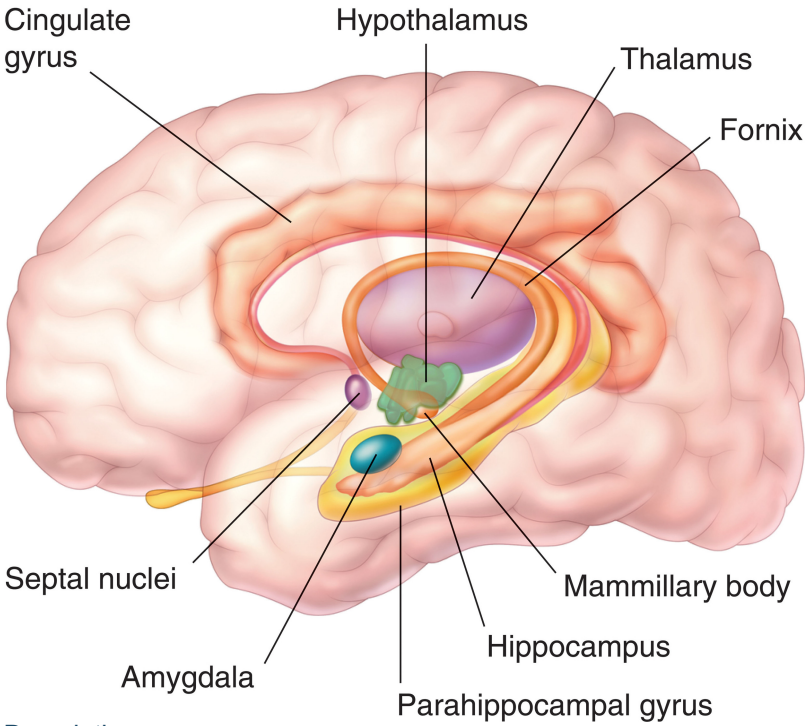
Some researchers suggest that feedback from emotional expressions has another role besides contributing to our emotional experience, in that it also helps us understand other people's emotions; this ability is critical to social communication and to societal success. This view is supported by studies of **mirror neurons**, which are neurons that fire both when we engage in a specific act and while observing the same act in others. They were first discovered when researchers noticed that neurons that were active while monkeys reached for food also responded when the monkeys saw the researcher picking up a piece of food (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992); similar correlations have been observed in other brain areas, including those involved in emotions (see review in Bastiaansen, Thioux, & Keysers, 2009). Observing another person's emotional expressions activates emotional areas in our own brains, and the amount of activity is related to scores on a measure of empathy (Chakrabarti, Bullmore, & Baron-Cohen, 2006).

Our observation of other people's emotions is not entirely passive; we also mimic their gestures, body posture, tone of voice, and (often imperceptibly) facial expressions (Bastiaansen et al., 2009). Just as feedback during our own emotional activity adds to our own emotional experience, feedback from imitated expressions may help us empathize with the emotions of others. Indeed, interfering with facial mimicry by engaging the required muscles in other activities (such as chewing gum) impairs participants' ability to recognize happiness and disgust in photos (Oberman, Winkielman, & Ramachandran, 2007). Women who have Botox treatments also rate facial photos and sentences as less emotional than before treatment (Baumeister, Papa, & Foroni, 2016). People with autism typically have trouble understanding other people's emotions, perhaps in part because their imitation of emotional expressions is delayed by about 160 milliseconds (Oberman, Winkielman, & Ramachandran, 2009).

A system this complex requires an equally complex control system. We will turn our attention now to the brain structures responsible for emotion.

The Emotional Brain

In the late 1930s and 1940s, researchers proposed that emotions originated in the **limbic system**, a network of structures arranged around the upper brain stem. We now know that emotion is more complex than envisioned then, but the limbic system continues to be a focus of interest because of its role not only in emotion but in motivation, learning, and memory. In the following pages, we will be discussing several of the limbic structures in Figure 8.4, along with others.



Description

Figure 8.4 Structures of the Limbic System.

? What are some of the brain structures involved in emotions, and what are their functions?

Much of what we know about the brain's role in emotion comes from lesioning and stimulation studies with animals; this research is limited because we do not know what the animal is experiencing. Fortunately, researchers have sometimes had the opportunity to study human patients with electrodes implanted in the brain, either for therapeutic stimulation or to aid in distinguishing between diseased and healthy areas prior to surgery. Robert Heath did some of the pioneering work in 1964 when he stimulated the brains of patients in an attempt to treat epilepsy, sleep disorders, or pain that had failed to respond to conventional treatments. Depending on the electrode's location, he found he could produce feelings of fear, rage, pleasure, and so on. Stimulation of the septal nuclei, for example, produced a sense of pleasure, accompanied by sexual fantasies and arousal. During stimulation, one patient went from near tears while talking about his father's illness to a broad smile as he described how he planned to take his girlfriend out and seduce her. When asked why he changed the subject, he replied that the thought just came into his head. Now researchers are more likely to use one of the scanning techniques to study the brain centers of emotion. Typically, they do MRI scans to determine the location of damage in patients with emotional deficits, or they use positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) while healthy participants relive an emotional experience, examine facial expressions of emotion, or view an emotional video.

Before we go too far in assigning emotions to specific brain structures, we need to emphasize that any emotion involves activity in a network that includes many areas of the brain (see Figure 8.5). Studies using fMRI and recordings from electrodes implanted prior to surgery in epilepsy patients show that each emotion produces its own characteristic pattern of activity that engages widespread areas of the brain (Saarimäki et al., 2018; Sani et al., 2013). With the understanding that no emotion can be relegated to a single part of the brain, we will look more closely at four areas that have particularly important roles in emotional experience and behavior: amygdala, prefrontal cortex, anterior insular cortex, and anterior cingulate cortex.

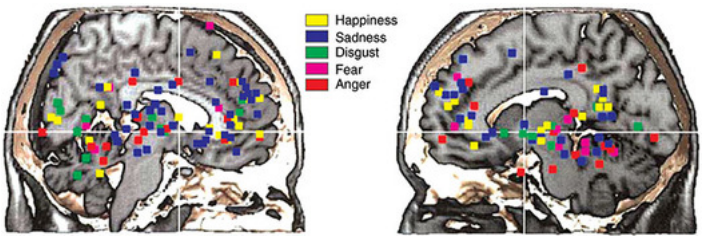
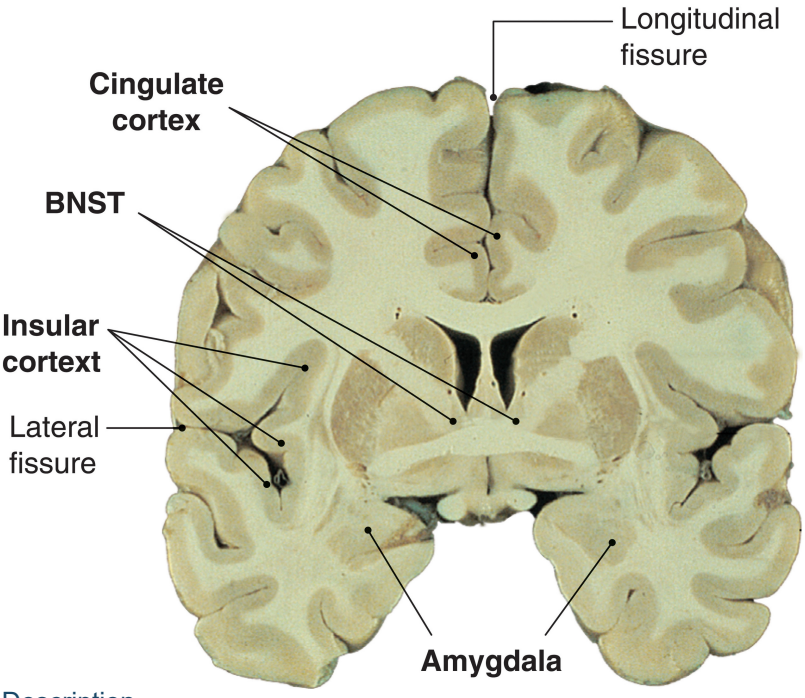


Figure 8.5 Brain Areas Activated During Different Emotions.
Each colored square represents the location identified in a single study for a particular emotion. In spite of the clustering of control of each emotion in a general area, the scattered dots of the same color indicate that each emotion relies on activity in multiple areas.

Source: Reprinted from "Functional Neuroanatomy of Emotion: A Meta-Analysis of Emotion Activation Studies in PET and fMRI," by K. L. Phan, T. Wager, S. F. Taylor, and I. Liberzon, *Neuroimage, 16*, pp. 331–348. Copyright 2002, with permission from Elsevier.

The Amygdala

The **amygdala** is a small, almond-shaped limbic system structure near the lateral ventricle in each temporal lobe (Figure 8.6). It is involved in a variety of emotions, but its participation in fear, anxiety, and aggression has been researched most thoroughly. People with the short allele of the *SLC6A4* gene have reduced serotonin activity; as a result, they are prone to fear and anxiety, and their amygdala is hyperresponsive to fear stimuli (Figure 8.7; Hariri et al., 2002). The medial part of the amygdala determines whether a situation is safe or threatening and then regulates approach and avoidance. By exposing mice to the odor of a predator or to a robotic "bug," Samara Miller and her team learned that the medial amygdala stimulates the ventromedial hypothalamus to produce avoidance or elicits approach and exploration by inhibiting the bed nucleus of the stria terminalis (BNST; S. M. Miller, Marcotulli, Shen, & Zweifel, 2019).



Description

Figure 8.6 Amygdala, BNST, Insular Cortex, and Cingulate Cortex.

Source: Photo Courtesy of Dana Copeland

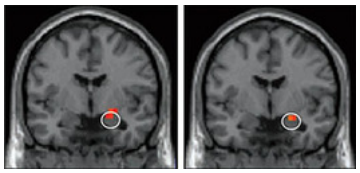


Figure 8.7 Activity in the Right Amygdala While Viewing Facial Expressions of Fear. The individual on the left has the short allele of the *SLC6A4* gene, which reduces serotonin activity and increases fear responsiveness; the one on the right has two copies of the long allele.

Source: Hariri et al., "Serotonin Transporter Genetic Variation and the Response of the Human Amygdala," *Science, 297*, pp. 400-403. Copyright 2002. Reprinted by permission of AAAS.

Rats with amygdala damage are so fearless they will not only approach a sedated cat but also climb all over its back and head (D. C. Blanchard & Blanchard, 1972). One rat even nibbled on the stuporous cat's ear, provoking an attack—and after the attack ended, the rat climbed right back onto the cat. A few humans have sustained damage to both amygdalas, usually as a result of infection or disease, and they also show a variety of deficits; like the rats, for example, they are unusually trusting of strangers (Adolphs, Tranel, & Damasio, 1998). Patients with damage to both amygdalas often live in supervised care, because their actions can easily bring harm to themselves and others.

S. M. is one of the best characterized patients with bilateral amygdala damage (Figure 8.8); she reported very little feeling of fear, and—in spite of having been held up at knifepoint, nearly killed in an act of domestic violence, and threatened with death on other occasions—her behavior never reflected any sense of desperation or urgency (Feinstein, Adolphs, Damasio, & Tranel, 2011). Researchers were unable to find any stimulus that could evoke fear in her; she was undisturbed by horror movies or a haunted house that produced screams in her companions, and she showed an unusual compulsion to touch snakes she had been told were deadly. Interestingly, during a test that involved inhaling carbon dioxide, which produces a feeling of suffocation, she and a similar patient experienced full-blown panic attacks (Feinstein et al., 2013). The researchers' interpretation was that the amygdala monitors external threats from the environment, and that fear triggered internally—in this case, by the sense of suffocation—has another neural basis.

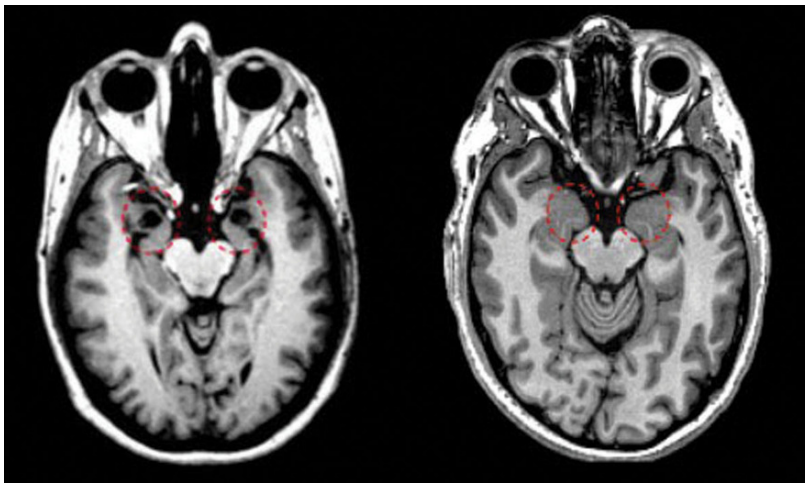


Figure 8.8 S. M.'s Brain, Compared With a Normal Brain.
In S. M.'s brain (left), you see only two dark voids (in the red circles) where each

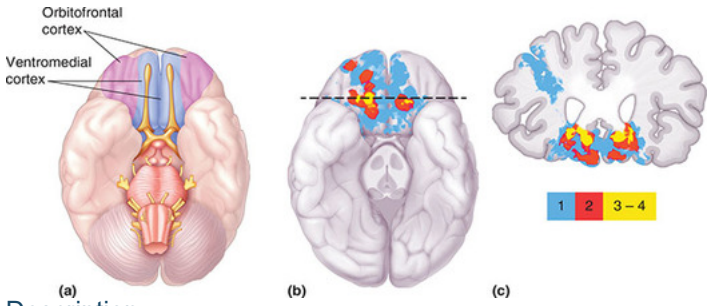
amygdala was before disease caused their deterioration. The brain on the right is normal, for comparison.

Source: From "Human Brain Is Divided on Fear and Panic: New Study Contends Different Areas of Brain Responsible for External Versus Internal Threats," by John Riehl, April 2, 2013, *Iowa Now*, retrieved from http://now.uiowa.edu/2013/01/human-brain-divided-fear-and-panic.

The amygdala is responsible for a variety of emotions, not just fear. Shuo Wang used fMRI to monitor activity in the amygdala while participants viewed photos of either fearful or happy faces expressing different emotions. The results showed that different neurons respond to these two emotions (S. Wang et al., 2014; S. Wang et al., 2017). The amygdala has other functions as well. In Chapter 7, you learned that the amygdala responds to sexually exciting stimuli; the following discussion describes a role in risk assessment and decision making; and in Chapter 12, you will see that it participates in memory formation, especially when emotion is involved.

The Prefrontal Cortex

The prefrontal cortex (see Figure 3.8 for location) receives much of its information from the amygdala, and it is the final destination for most of the brain's information about emotion before action is taken. You saw in Chapter 3 that damage to the prefrontal area or severing its connections with the rest of the brain impairs people's ability to make rational judgments. Later in this chapter, you will learn that people with deficiencies in the area are unable to restrain violent urges, and in Chapter 14, you will see that abnormalities in the prefrontal area also figure prominently in depression and schizophrenia. These deficits have a variety of causes, including injury, infection, tumors, strokes, and developmental errors. What the victims have in common is damage to the prefrontal area that includes the ventromedial cortex and the orbitofrontal cortex (see Figure 8.9).

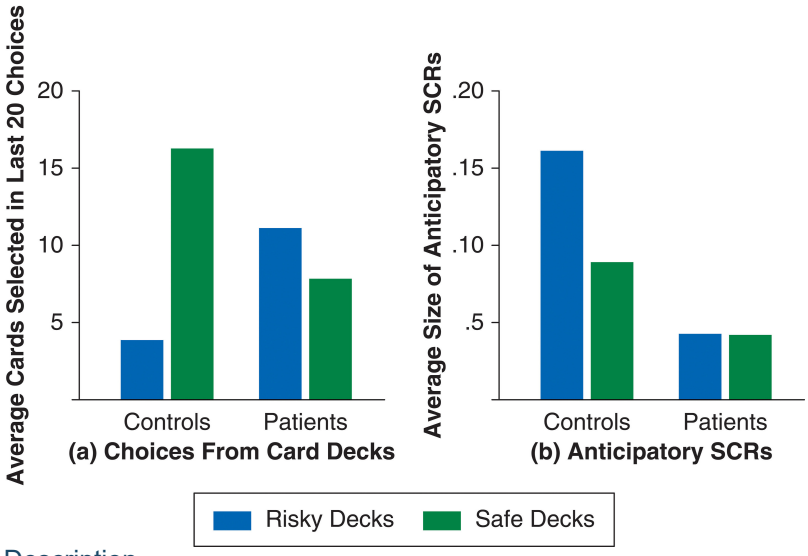


Description

Figure 8.9 Location of Damage That Impairs Emotion-Based Decision Making. In (a) the location of the ventromedial cortex and the orbitofrontal cortex is shown. In (b) you can see where damage occurred in four patients who showed judgment problems. The horizontal line shows where the scan in (c) was taken. In (b) and (c), the different colors indicate the number of patients with damage in the area, according to the code on the color bar. All shared damage in the ventromedial cortex, but some had damage in the orbitofrontal cortex as well.

The prefrontal cortex makes the final determination whether to produce a given behavior, using information supplied by other brain areas about the relative value of the choices, the likelihood of success, and the cost of failure. From this description, it is easy to see why most research on decision making is done in the form of studies of risk taking. A good example is a gambling task study in which healthy volunteers and patients with damage to the ventromedial prefrontal cortex chose cards from four decks to win play money (Bechara et al., 1999). Initially, both groups chose more often from the two "risky" decks, which usually resulted in large rewards but occasionally led to large penalties, for an overall loss. Over time, members of the control group shifted to the two "safe" decks, whose cards produced lower rewards

and smaller penalties for an overall gain; the patients typically did not make the shift, however, even after they figured out how the game worked (Figure 8.10a).



Description

Figure 8.10 Comparison of Gambling Task Behavior in Controls and Patients With Damage to the Prefrontal Cortex.
The controls shifted from preferring cards from the risky decks to preferring cards from the safe decks, but the patients did not. (b) Also, as the task progressed, only the controls showed anticipatory skin conductance responses (SCR) before choosing from the risky decks.

? How does loss of emotion impair "rational" decision making?

To assess emotional responses during the task, the researchers used the **skin conductance response (SCR)**, a measure of sympathetic nervous system activity obtained by recording changes in the skin's electrical conductance that occur during sweat gland activation. Both groups showed emotional reactions—increases in skin conductance—when their choices resulted in wins or losses. And over time, the controls began to show anticipatory SCRs just before drawing a card from a risky deck, even before they were able to verbalize that those stacks were risky. (This is the example of unaware emotional influence we promised earlier.) The patients, however, did not produce these anticipatory responses; although their bad choices, once made, elicited emotional responses, their prefrontal damage made them unable to process the consequences of risky behavior and use that information to modify their choices (Figure 8.10b).

The evolutionary value of emotion is that it drives us to make approach and avoidance responses; it helps guide us in making decisions important to our survival. The prefrontal cortex uses information from other areas, including the nucleus accumbens, amygdala, and posterior parietal cortex, in making decisions. The amygdala evaluates the emotional content of a situation, while the nucleus accumbens assesses the potential reward value of an action. Functional connectivity is stronger between the prefrontal cortex and the amygdala and nucleus accumbens in teens identified as risk takers (DeWitt, Aslan, & Filbey, 2014) and in individuals who choose larger but unpredictable (risky) rewards over small but certain rewards (W. H. Jung, Lee, Lerman, & Kable, 2018). Some of the participants in Bechara's card study had bilateral amygdala damage. Like the prefrontal patients, they failed to produce anticipatory SCRs when choosing from the risky decks, but they also didn't respond to monetary gains and losses. While the prefrontal patients couldn't make use of emotional information from the amygdala about rewards and punishments, the amygdala-damaged patients couldn't generate an emotional response in the first place.

Stimulating the nucleus accumbens in patients with electrodes implanted for therapeutic purposes caused them to make riskier choices in a monetary reward game (Nachev et al., 2015). Evidence suggests this increase in risky behavior is due to enhanced reward sensitivity (Telzer, Ichien, & Qu, 2015). Studies with rats indicate that risky versus safe behavior depends on whether stimulation occurs in the core or the shell of the nucleus accumbens, and whether D_1 or D_2 receptors are activated (Floresco, Montes, Maric, & van Holstein, 2018; Stopper, Khayambashi, & Floresco, 2013).

The posterior parietal cortex determines the probability of reward before the prefrontal cortex decides whether to act. Patients with damage to this area often made large bets when the odds were low and small bets when the chances of winning were strongly favorable (Studer, Manes, Humphreys, Robbins, & Clark, 2015). Risk taking is correlated with posterior parietal gray matter volume (Gilaie-Dolan et al., 2014), and the two decline together with age (Grubb, Tymula, Gilaie-Dolan, Glimcher, & Levy, 2016).

The prefrontal cortex's connections to other parts of the brain also determine whether we are novelty-seeking adventurers or are more restrained, as A Further Look explains.

A Further Look:

Why Bob Doesn't Jump Out of Airplanes

Source: © iStockphoto.com/vuk8691

In our discussion of sensation seeking in Chapter 6, we mentioned the first author's wife's skydiving adventure. Why did she enjoy leaping out of a perfectly good airplane at 14,000 feet, while he preferred to stay on the ground and take photos of her descent? Why did she like to travel to exotic places, such as Thailand and Patagonia, while he would rather stay at home and write about behavioral neuroscience? Once again, research comes to the rescue. Psychologists at the University of Arizona (M. X. Cohen, Schoene-Bake, Elger, & Weber, 2009) used a questionnaire to categorize 20 volunteers as novelty seekers (agreeing to statements such as "I like to try new things just for fun") or reward dependent (agreeing to statements such as "I'd rather stay home than go out"). Novelty seekers are higher in exploratory drive and impulsivity, whereas those considered reward dependent spend a lot of time pursuing activities that have been rewarding in the past instead of trying new things.

Next, the researchers used diffusion tensor imaging to measure the density of the participants' white-matter tracts. Their analysis focused on the hippocampus, amygdala, and striatum (which includes the nucleus accumbens), because animal research has indicated that these structures form a looping circuit that is important in

novelty seeking. There were strong white-matter connections within this loop in the human novelty seekers, but the reward-dependent volunteers' strongest connections were between the striatum and prefrontal areas, which apparently put the brakes on risky behavior.

Just before the skydiving experience, the jump videographer interviewed Bob's wife about why she was making the jump, then turned the camera on Bob and asked why he chose not to. He answered lamely, "I just don't need to." Today, armed with the results of this study, his answer would be, "My prefrontal cortex won't let me!"

Anterior Insular Cortex and Anterior Cingulate Cortex

Looking back at Figure 8.6, you can see that the insular cortex is located deep inside the lateral fissure, and the cingulate cortex is located on the two gyri that lie above the corpus callosum. The anterior insular cortex (AIC) was long regarded as no more than a sensory projection area for the viscera. It does monitor all manner of internal conditions, but as you can appreciate from our earlier discussion about how internal information contributes to emotional experience, it responds to all subjective feelings, including emotions (A. D. Craig, 2009). The **anterior cingulate cortex (ACC)**, best known for its roles in attention, decision making, and impulse control, also plays a major role in emotion (Figures 8.4 and 8.11). The ACC is intimately connected with the AIC, and the two form a network with the amygdala and hypothalamus; in almost all recent imaging studies of emotion, the two were activated simultaneously during the experience of emotional feelings (A. D. Craig, 2009; Gu, Hof, Friston, & Fan, 2013). The range of emotions detected there is remarkably broad, including the basic emotions of love, anger, fear, sadness, and happiness and the more complex experiences of empathy, aversion, unfairness, uncertainty, trust, and disbelief.

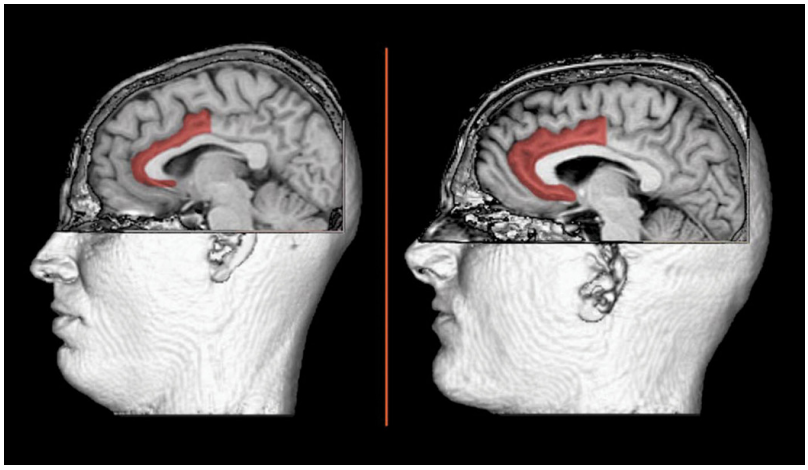


Figure 8.11 Size Differences in the Anterior Cingulate Gyrus.
A larger anterior cingulate gyrus (highlighted in red) is associated with a higher level of the personality characteristic of harm avoidance.

Source: From "Anatomical Variability of the Anterior Cingulated Gyrus and Basic Dimensions of Human Personality," by J. Pujol et al., *Neuroimage, 15*, pp. 847–855, fig. 1, p. 848. © 2002. Used with permission from Elsevier.

Many researchers consider the AIC and the ACC of primary importance in the *conscious experience* of emotions. We can think of the AIC as the limbic sensory structure and the ACC as the limbic motor structure. The AIC is considered to be the location, or at least *a* location, of emotion awareness; the ACC, with its outputs to prefrontal cortex and cortical motor areas, is believed to use input from the AIC to generate action. *Alexithymia*, a deficit in the ability to identify and describe emotions experienced by one's self or others, occurs in 10% of the population and in 85% in individuals with autism spectrum disorder, where it is correlated with reduced gray

matter and reduced activity in the AIC. It is also seen in patients with frontotemporal dementia and is associated with degeneration of the insular and cingulate cortices (A. D. Craig, 2009; Gu et al., 2013).

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- Describe the role of the autonomic nervous system in emotion (including the possible identification of emotions).
- Organize your knowledge: List the major parts of the brain described in this section that are involved in emotion, along with their functions.
- How are the effects of prefrontal and amygdala damage alike, and how are they different?

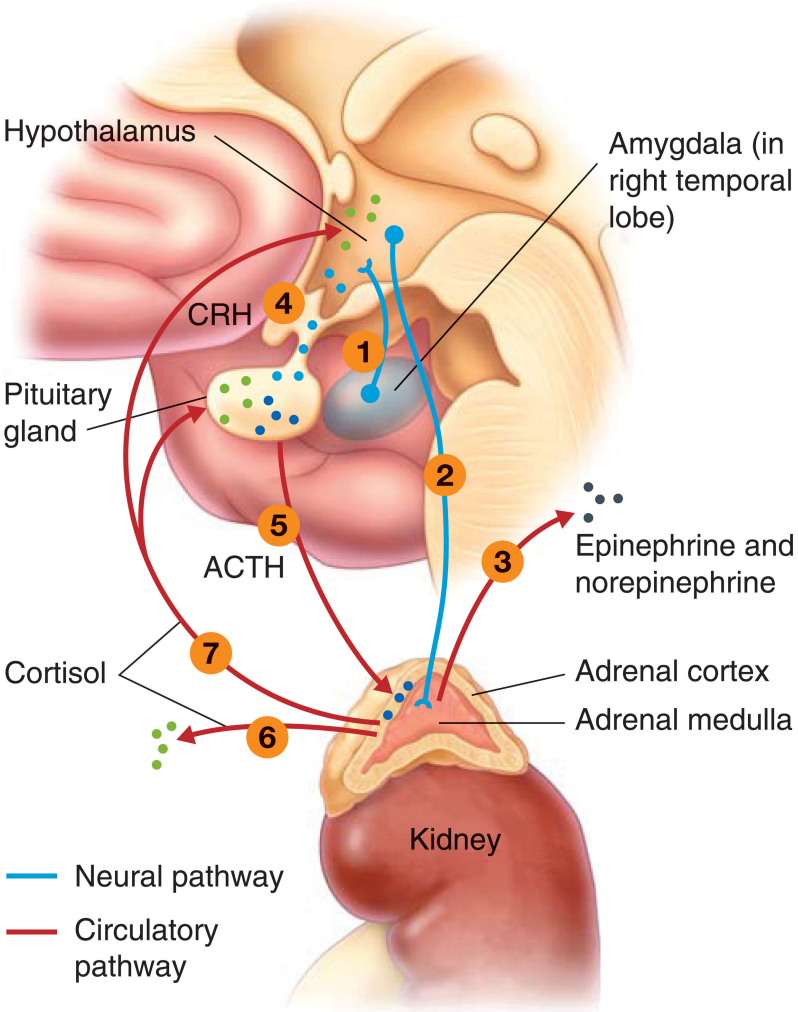
STRESS, IMMUNITY, AND HEALTH

Stress is a term that has two meanings in psychology. **Stress** is a condition in the environment that makes unusual demands on the organism, such as threat, failure, or bereavement. Stress is also an internal condition, your response to a stressful situation; you *feel* stressed, and your body reacts in several ways. Whether a situation is stressful to the person is often a matter of individual differences, either in perception of the situation or in physiological reactivity. For some people, even the normal events of daily life are stressful, whereas others thrive on excitement and would feel stressed if they were deprived of frequent challenges. In other words, stress in this sense of the term is in the eye of the beholder.

? What are the positive effects of stress?

Stress as an Adaptive Response

The body's short-term response to a stressful situation is positive and adaptive. When the amygdala signals the hypothalamus that a stressful event has occurred, the hypothalamus activates the sympathetic system by stimulating the adrenal medulla to release epinephrine and norepinephrine into the bloodstream. The resulting increases in heart rate, blood pressure, and respiration rate mobilize the individual for "fight-or-flight" and inhibit non-adaptive functions, such as digestion and sexual arousal. The stress response is further augmented about 10 seconds later by the **hypothalamus-pituitary-adrenal axis**, which consists of the hypothalamus, pituitary gland, and adrenal glands (Figure 8.12). The hypothalamus secretes corticotropin-releasing hormone through the portal to the pituitary gland, causing the pituitary to release adrenocorticotropic hormone into the bloodstream. At the adrenal glands, adrenocorticotropic hormone stimulates the adrenal cortex to release glucocorticoids, including cortisol, into the bloodstream. **Cortisol**, the most abundant glucocorticoid in humans, produces additional physiological stress responses, including increases in metabolism, glucose availability, and blood supply to the skeletal muscles. The effects of cortisol are more sustained than those of epinephrine and norepinephrine. Cortisol also provides negative feedback to various levels of the axis, moderating the stress response (Mah, Szabuniewicz, & Fiocco, 2016). Before we leave this topic, there's a surprising new finding about how puffer fish avoid stress in A Further Look.



Description

Figure 8.12 The Hypothalamus-Pituitary-Adrenal Axis.
The amygdala signals a stressful condition to the hypothalamus (1), which stimulates the adrenal medulla (2), which then releases epinephrine and norepinephrine into the bloodstream (3), enabling the "fight or flight" response. The hypothalamus activates the hypothalamus-pituitary-adrenal axis by secreting CRH (corticotropin-releasing hormone) via the portal to the pituitary gland (4), causing the pituitary to release ACTH (adrenocorticotropic hormone) into the bloodstream (5). The adrenal cortex releases cortisol into the bloodstream, producing physiological stress responses (6). Cortisol also provides negative feedback, moderating the stress response (7).

Carolina Hrejsa/Body Scientific Intl.

A Further Look:

How Puffer Fish Manage Stress

Remember the toxic puffer fish from Chapter 2? Their tetrodotoxin (TTX) is an effective deterrent to hungry predators, but is that its only function? Puffers don't make their own TTX but instead accumulate it from TTX-making bacteria in their diet. Laboratory puffers get a processed food that doesn't have the bacteria, so they lack TTX, which makes them ideal for answering the question. A team of Japanese

researchers fed laboratory puffer fish with purified TTX for a month; they grew 6% longer and 24% heavier than the fish raised on a TTX-free diet (Amano et al., 2019). The TTX-enhanced group also were less aggressive toward their tank mates. Both growth rate and aggression are influenced by stress, but this alone doesn't mean that the results are due to stress reduction. The clincher came when the researchers looked at the puffers' hormone levels. The fish that lacked TTX had higher levels of corticotropin-releasing hormone in their brains and four times as much cortisol compared to the TTX-enhanced fish.

Brief stress increases activity in the **immune system**, the cells and cell products that kill infected and malignant cells and protect the body against foreign substances, including bacteria, viruses, toxins, and pollen (Herbert et al., 1994). **Leukocytes**, or white blood cells, detect invaders by the unique proteins that every cell has on its surface and attacks and destroys them. A type of leukocyte called a **macrophage** ingests intruders and then displays the intruder's antigens—substances that produce an immune response—on its own cell surface (Figure 8.13). These antigens attract T cells to the area. The **T cell** is another leukocyte; it has four types, which either kill invaders or help regulate the immune system. The **B cell**, a third type of leukocyte, fights intruders by producing antibodies that attack a specific cell type. The **natural killer cell** attacks and destroys certain kinds of cancer cells and cells infected with viruses. The brain and spinal cord are considered "immune privileged," in that the central nervous system is protected from most infectious agents by the blood-brain barrier. When these agents do make their way in, they are dealt with by **microglia**, which act in most ways like macrophages by ingesting invaders and attracting T cells. Table 8.1 summarizes the characteristics of these immune cells.

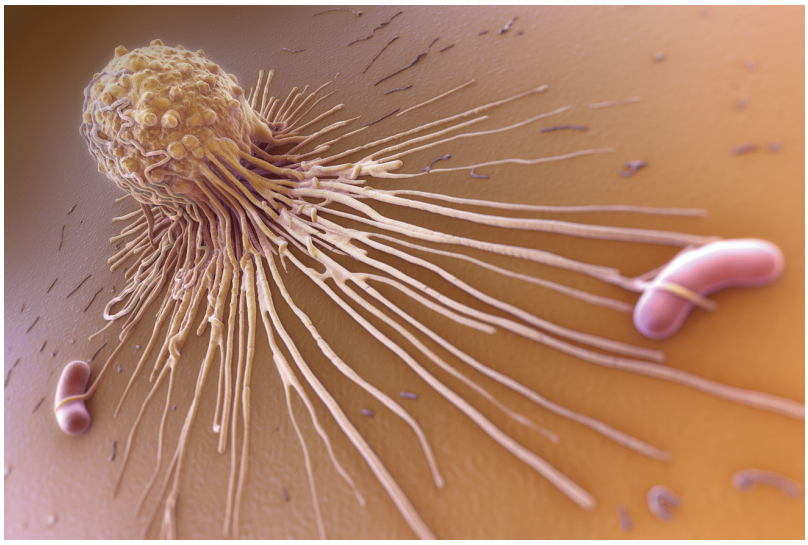


Figure 8.13 Macrophage Preparing to Engulf Bacteria.
A macrophage, a type of white blood cell, is stretching out projections that will eventually engulf and digest bacterial cells.

Source: Science Picture Co/Science Source

Table 8.1

TABLE 8.1 Major Types of Immune Cells.

LEUKOCYTES				
Macrophages	T Cells	B Cells	Natural Killer Cells	Microglia
Ingest invaders; display antigens, which attract T cells.	Attack invaders and regulate immune system.	Make antibodies, which destroy intruders.	Attack cells containing viruses and certain kinds of tumor cells.	Ingest invaders in brain and spinal cord; display antigens to attract T cells.

Some antibodies are transferred from mother to child during the prenatal period or postnatally through the mother's milk. Most antibodies, though, result from a direct encounter with invading organisms, for example, during exposure to measles.

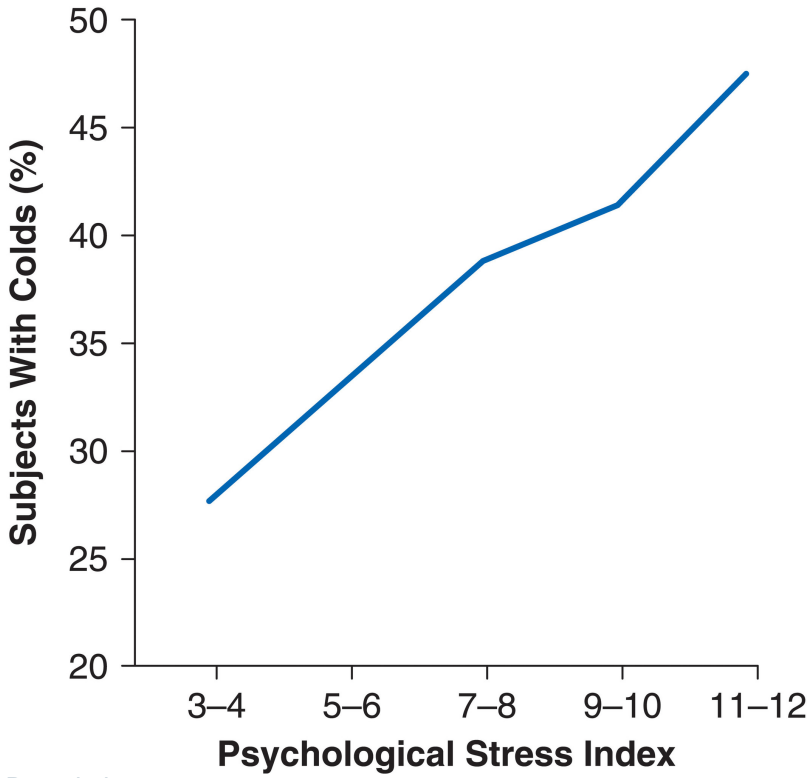
Vaccinations work because injection of a weakened form of the disease-causing bacteria or virus triggers the B cells to make antibodies for that disease.

The preceding is a description of what happens when all goes well. In the immune deficiency disease AIDS (acquired immune deficiency syndrome), by contrast, T cells fail to detect invaders, and the person dies of an infectious disease. In an **autoimmune disorder**, the immune system runs amok and attacks the body's own cells. In the autoimmune disorder multiple sclerosis, for instance, the immune system destroys myelin in the central nervous system.

Negative Effects of Stress

We are much better equipped to deal with brief stress than with prolonged stress. Chronic stress can interfere with memory, increase or decrease appetite, diminish sexual desire and performance, deplete energy, and cause mood disruptions. And while brief stress enhances immune activity, prolonged stress compromises the immune system. After an accident at the Three Mile Island nuclear electric plant released radiation into the surrounding atmosphere, nearby residents had elevated stress symptoms and performed less well on tasks requiring concentration compared with people who lived outside the area (Baum, Gatchel, & Schaeffer, 1983). Amid concerns about continued radioactivity and the long-term effects of the initial exposure, residents had reduced numbers of B cells, T cells, and natural killer cells as long as 6 years after the accident (McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989).

Disease symptoms were not measured at Three Mile Island, but other studies have found that health is compromised when stress impairs immune functioning. Recently widowed women experienced decreased immunity and marked health deterioration in the year following the spouse's death (Maddison & Viola, 1968). Also, students have reduced immune responses, more infectious illnesses, and slower wound healing at exam times than at other times of the year (Glaser et al., 1987; Marucha, Kiecolt-Glaser, & Favagehi, 1998). In a rare experimental study, healthy individuals were given nasal drops containing common cold viruses and then were quarantined and observed for infections. In Figure 8.14, you can see that their chance of catching a cold depended on the level of stress they reported on a questionnaire at the beginning of the study (S. Cohen, Tyrrell, & Smith, 1991). In a follow-up study, it turned out that only stresses that had lasted longer than a month increased the risk of infection (S. Cohen et al., 1998).



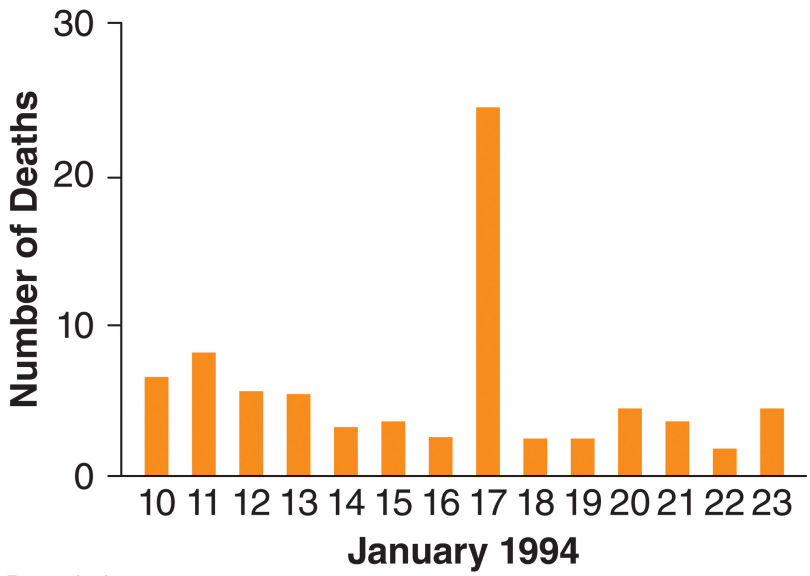
Description

Figure 8.14 Relationship Between Stress and Vulnerability to Colds.

Source: Adapted from "Psychological Stress and Susceptibility to the Common Cold," by S Cohen, A. D. Tyrrell, and A. P. Smith, *New England Journal of Medicine, 325*, pp. 606-612. © 1991 Massachusetts Medical Society. All rights reserved.

The cardiovascular system is particularly vulnerable to stress. Stress increases blood pressure, and prolonged high blood pressure can damage the heart or cause a stroke. Some people are more vulnerable to health effects from stress than others. Researchers classified young children as normal reactors or excessive reactors based on their blood pressure increases while one hand was immersed in ice water. Forty-five years later, 71% of the excessive reactors had high blood pressure, compared with 19% of the normal reactors (Wood, Sheps, Elveback, & Schirger, 1984).

The cardiovascular system is also very susceptible to acute stress, which in some cases can result in death. This fact has not always been accepted in the scientific and medical communities, but in 1942, the physiologist Walter Cannon determined that reports of apparent stress-related deaths were legitimate. He even suggested that *voodoo death*, which has been reported to occur within hours of a person being "hexed" by a practitioner of this folk cult, is also due to stress. We now know that fear, loss of a loved one, humiliation, or even extreme joy can result in sudden cardiac death. In **sudden cardiac death**, the excessive sympathetic activity that accompanies stress sends the heart into fibrillation, contracting so rapidly that it pumps little or no blood. When one of the largest earthquakes ever recorded in a major North American city struck the Los Angeles area in 1994, the number of deaths from heart attacks increased five-fold (Figure 8.15; Leor, Poole, & Kloner, 1996).



Description

Figure 8.15 Increase in Cardiac Deaths on the Day of an Earthquake.

Source: Reprinted from J. Leor, W. K. Poole, & R. A. Kloner, "Sudden Cardiac Death Triggered by an Earthquake." *New England Journal of Medicine, 334*, pp. 413-419. © 1996 Massachusetts Medical Society. All rights reserved.

The stress doesn't have to be as extreme as an earthquake: During the 2006 soccer World Cup games in Germany, cardiac emergencies in that country tripled in men and almost doubled in women (Wilbert-Lampen et al., 2008); when the Los Angeles Rams were defeated in the 1980 Super Bowl, cardiac deaths in the team's hometown increased 15% in men and 27% in women (Kloner, McDonald, Leeka, & Poole, 2011). Heart attack rates even increase following the spring change to daylight savings time, as people cope with earlier wake times and minor sleep deprivation, and then drop slightly when the autumn transition gives them an extra hour of sleep (I. Janszky & Ljung, 2008; Sandhu, Seth, & Gurm, 2014).

Chronic stress can produce structural and functional degeneration in the brain. An fMRI study showed that adults who had grown up in poverty were more likely to have an overly active amygdala and an underactive prefrontal cortex, along with difficulty suppressing negative emotions (P. Kim et al., 2013). Prolonged stress increases dendritic growth in the amygdala and produces a loss of dendrites in the prefrontal cortex, which impairs its ability to regulate the amygdala (Mah et al., 2016). But the most documented damage from stress involves the hippocampus (Figure 8.16). For example, hippocampal volume was reduced in Iraqi combat veterans, and the volume was inversely related to the perceived threat during deployment (Grupe et al., 2019). Hippocampal reduction is also seen in adults who experienced childhood adversity, including poverty, neglect, and physical, emotional, and sexual abuse (Calem, Bromis, McGuire, Morgan, & Kempton, 2017), and in victims of psychological and physical torture (Zandieh et al., 2016) The torture victims also had reduced gray matter volume. There is evidence that chronic excess cortisol can cause hippocampal damage: Implanting cortisol pellets in monkeys' brains damaged their hippocampi (Sapolsky, Uno, Rebert, & Finch, 1990), and elderly humans who had elevated cortisol levels over a 5-year period had an average 14% decrease in hippocampal volume (Lupien et al., 1998). Remember, though, that cortisol's effect at the time of trauma is adaptive, enabling the person to cope with the stressor. In fact, low cortisol at the time of trauma is predictive of later development of posttraumatic stress disorder (PTSD), and administration of hydrocortisone immediately after trauma reduces the chance of developing PTSD (Costa, 2016). A Further Look describes remarkable evidence of brain damage following two major disasters.

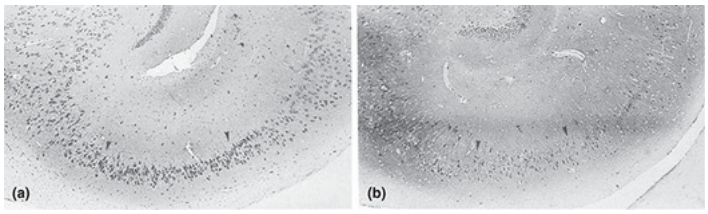


Figure 8.16 Hippocampal Damage in a Stressed Monkey.
Compare the number of cells between the arrows in the hippocampus of a control monkey (a) and the number in the same area in a monkey that died spontaneously of apparent stress (b).

Source: "Hippocampal Damage Associated With Prolonged and Fatal Stress in Primates," by H. Uno, R. Tarara, J. G. Else, M. A. Suleman, & R. M. Sapolsky, 1999, Journal of Neuroscience, 9, 1705–1711. Copyright (1999) Society for Neuroscience. Reprinted with permission.

Several studies suggest that reducing stress can improve health. T cell counts increased in AIDS patients after 20 hours of relaxation training (D. N. Taylor, 1995); similar training was associated with reduced death rates in elderly individuals (C. N. Alexander, Langer, Newman, Chandler, & Davies, 1989) and in cancer patients (Fawzy et al., 1993; Spiegel, 1996). However, evidence that survival rate in these studies is related to immune function improvement is sketchy (Fawzy et al., 1993); it is possible that study participation led the elderly participants and cancer patients to make lifestyle changes.

? In what ways do personality characteristics influence immune functioning?

Social, Personality, and Genetic Factors

Research has found a variety of associations between personality characteristics and vulnerability to or protection against disease (Sutin, Zonderman, Ferrucci, & Terracciano, 2013). As examples, type D "distressed" personality has been linked to increased risk for cardiovascular disease (Sahoo, Padhy, Padhee, Singla, & Sarkar, 2018), and HIV-infected individuals were found to have eight times higher HIV levels if they were introverted (S. W. Cole, Kemeny, Fahey, Zack, & Naliboff, 2003). Social environment appears to be important as well: People who have a network of relationships with family, friends, and community are healthier and live longer than those who are socially isolated (Y. C. Yang et al., 2016).

Rather than accepting these relationships at face value, our job as neuroscientists is to discover the physiological mechanisms behind them. The HIV researchers pointed out that introverted individuals have elevated norepinephrine and that high levels of norepinephrine increase HIV replication. Autonomic activity was elevated in the introverted HIV patients (assessed from variability of heart rate, skin conductance, and other measures), confirming that increased norepinephrine was the probable link between their introversion and their elevated HIV burden (S. W. Cole et al., 2003). Research also shows that the health effects of social support are due, at least in part, to greater stress resistance and improved immune functioning (Ozbay et al., 2007; Uchino, Vaughn, Carlisle, & Birmingham, 2012). For example, in the aftermath of the Three Mile Island nuclear incident, residents with greater social support reported less stress and had lower levels of stress hormones (Fleming, Baum, Gisriel, & Gatchel, 1982).

Although we have gone one level deeper by identifying these physiological mediators, these correlations don't allow us to say that personality characteristics and social support are the *causes* of the observed health effects. A case in point is the high association between mood disorder and cancer, which led some researchers to conclude that depression is a predisposing factor. The opposite is more likely, because animal research indicates that immune system cytokines whose release is triggered by tumors can produce depressive-like behaviors (Pyter, Pineros, Galang, McClintock, & Prendergast, 2009). Likewise, a novel study with mice showed that

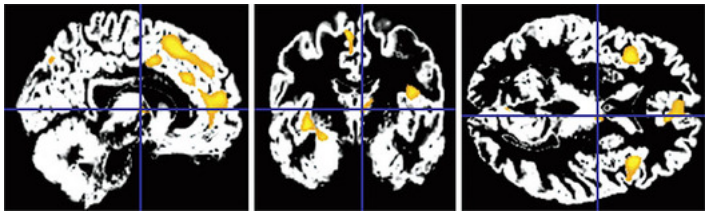
sociability is partly under the control of the immune system. Mice bred to lack the immunity molecule interferon gamma (IFN-γ) are socially deficient, spending no more time investigating another mouse than an inanimate object; replacing the molecule restores normal socialization (Figure 8.17; Filiano et al., 2016). Functional MRI scanning revealed that IFN-γ inhibits neurons in areas of the prefrontal cortex that are involved in social behavior, apparently turning off the risk aversion that would otherwise prevent social interaction. Apparently cause can work in the other direction as well. Housing mice in groups activates IFN-γ, and isolation deactivates it. Such an unexpected interaction between the immune system and social behavior begs explanation. The researchers suggest that IFN-γ co-evolved with social behavior in response to the increasing need for protection against communicable disease.

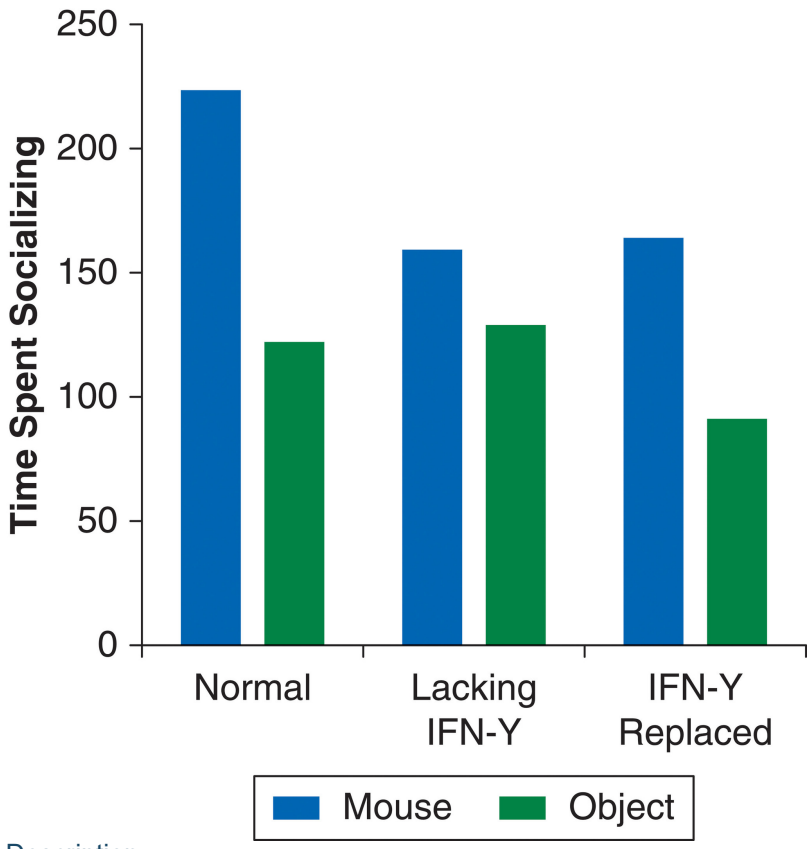
A Further Look:

One Aftermath of Disaster Is Stress-Related Brain Damage

Three years after the 9/11 terrorist attacks on the World Trade Center killed more than 2,700 people, researchers compared fMRI scans of people living within 1.5 miles (2.4 kilometers) of the towers with those of volunteers living 200 miles (322 kilometers) away (Ganzel, Kim, Glover, & Temple, 2008). Although the near residents did not qualify for a diagnosis of PTSD, they had reduced gray-matter volume in the hippocampus, amygdala, prefrontal cortex, ACC, and insula; in addition, amygdala activation was greater when they viewed facial expressions of fear (see figure).

Two studies of people affected by the devastating Japanese earthquake of 2011 had the rare advantage of being able to examine before-and-after brain scans. After the earthquake, researchers recruited 42 individuals who had received MRI scans as part of previous research and scanned them again (Sekiguchi et al., 2013). Stress-related symptoms were highest in those with lower gray-matter volume in the ACC prior to the quake and in those with greater pre-to-post loss of gray-matter volume in the orbitofrontal cortex (OFC). The researchers believed that due to the ACC's involvement in processing fear and anxiety, its small volume made the individuals vulnerable to developing OFC damage and stress symptoms. A year later, although OFC volumes had increased, right hippocampal volumes had decreased and symptoms were unchanged (Sekiguchi et al., 2014).





Description

Figure 8.17 Interferon-γ and Sociability in Mice.
Normal mice spent more time with other mice than objects, while animals lacking interferon gamma had little preference for mice over objects. When interferon was replaced in the mice, the social preference for other mice returned.

Source: Adapted from Filiano, A., Xu, Y., Tustison, N. et al. Unexpected role of interferon-γ in regulating neuronal connectivity and social behaviour. Nature 535, 425–429 (2016).

Personality characteristics such as introversion are moderately heritable, and so is vulnerability to stress; for example, a study of 300 Swedish twins concluded that 32% of workplace stress is genetic (Judge, Ilies, & Zhang, 2012). One gene implicated in stress is *NPY*, which encodes the production of neuropeptide Y (which you know from its involvement in appetite). People with variants of the gene that result in low NPY production react to threat with exaggerated activity in the amygdala and the ACC (Reichmann & Holzer, 2016). Oxytocin not only promotes social bonding but also reduces stress responses such as heart rate and blood pressure. Individuals with the G allele of the *OXTR* receptor gene have a higher tendency to seek social support; unlike those with the A allele, they produce less cortisol in a stressful situation if they are in the company of a friend (F. S. Chen et al., 2011). MRI scans of individuals with a history of life stresses did not find reductions in hippocampal volume unless the individuals also had one of three gene variants previously associated with depression —*5-HTTLPR* (short allele), *COMT* (Val158Met), and *BDNF* (Val66Met; Rabl et al., 2014). The effects were cumulative, with greater decreases in participants who had more than one allele and a greater number of stresses. Interestingly, those with no genetic risk had enlarged hippocampi. The researchers speculated that the increases could be due to increased neurogenesis and neuroplasticity, which has been reported in response to low-dose glucocorticoids, predictable stress, and healthy coping behavior.

Not only do genes affect the stress response; stress in turn causes epigenetic changes in genes, and some of these changes are passed on to offspring. In January 1998, a 3-day ice storm in Quebec collapsed the electric power grid and left millions of people without electricity for more than a month. Thirteen years later, women who were pregnant at the time were asked to answer a questionnaire assessing the degree of objective hardship, such as number of days without power, injury, damage to the residence, and time in a shelter. Their scores on the questionnaire were correlated with the degree of DNA methylation in 957 genes in the T cells of their children (Cao-Lei et al., 2014). Even epigenetic changes resulting from early life stress in a parent can be passed on to offspring, at least in mice. And we have learned that similar changes are found in the sperm of men who experienced early life trauma, so the same is likely true for humans (Dickson et al., 2018). These changes were not in the form of methylation but involved altered expression in microRNAs, short fragments of non-coding RNA that regulate gene functioning. One microRNA has been specifically linked with stress: Research participants who showed more stress in a laboratory exercise were more likely to have greater expression in microRNA-29c, as well as increased connectivity between the ventromedial prefrontal cortex and the ACC (Vaisvaser et al., 2016).

Pain as an Adaptive Emotion

Eighty percent of all visits to physicians are at least partly to seek relief from pain (Gatchel, 1996), and we spend billions each year on nonprescription pain medications. These observations alone qualify pain as a major health problem.

A world without pain might sound wonderful, but in spite of the suffering it causes, pain is valuable for its adaptive benefits. It warns us that the coffee is too hot, that our shoe is rubbing a blister, that we should take our skis back to the bunny slope for more practice. People with **congenital insensitivity to pain**, a rare genetic disorder of the peripheral nervous system, are unable to sense pain; they injure themselves repeatedly because they are not motivated to avoid dangerous situations, and they die from untreated conditions, such as a ruptured appendix. Mild pain tells us to change our posture regularly; a woman with congenital insensitivity to pain suffered damage to her spine because she could not respond to these signals, and resulting complications led to her death (Sternbach, 1968).

Pain is one of the senses, a point we consider in more detail in Chapter 11. Here we focus on the feature that makes pain unique among the senses: It is so intimately involved with emotion that we are justified in discussing it as an emotional response. In fact, when we tell someone about a pain experience, we are usually describing an emotional reaction; it is the emotional response that makes pain adaptive.

There are many examples. Pain someone inflicts on you intentionally hurts more than pain you experience accidentally (K. Gray & Wegner, 2008). The perceived intensity of pain perception also is influenced by a person's ethnicity and culture (C. M. Campbell & Edwards, 2012). And as Beecher (1956) observed, "the intensity of suffering is largely determined by what the pain means to the patient" (p. 1609). After the landing at the Anzio beachhead in World War II, 68% of the wounded soldiers denied pain and refused morphine; only 17% of civilians with similar "wounds" from surgery accepted their pain so bravely. The soldiers were not simply insensitive to pain, because they complained bitterly about rough treatment or inept blood draws. According to Beecher, who was the surgeon in command at Anzio, the surgery was a major annoyance for the civilians, but the soldiers' wounds meant they had escaped the battlefield alive.

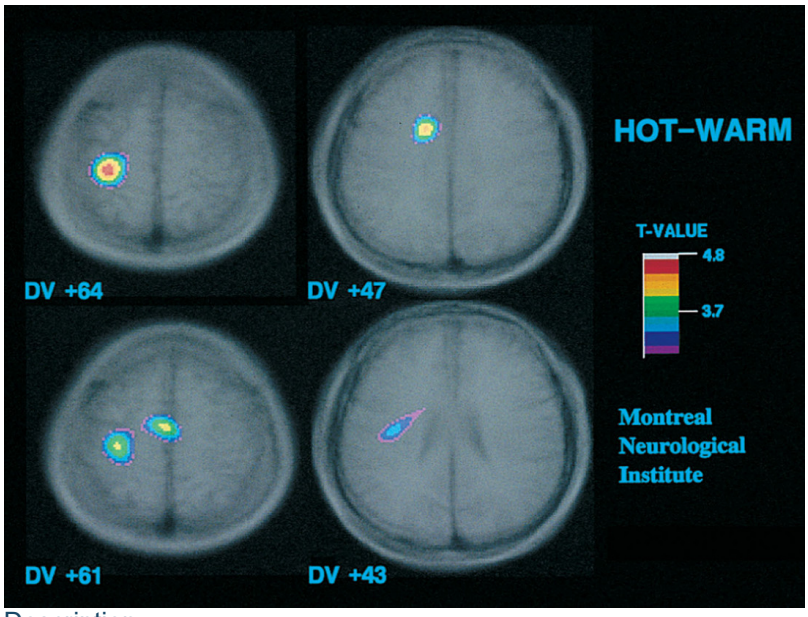
Spiritual devotion can influence the meaning of pain so that it is not felt or is endured for a higher purpose. Each spring in some remote villages of India, a man is suspended by a rope attached to steel hooks in his back; swinging above the cheering crowd, he blesses the children and the crops. Selection for this role is an honor, and the participant seems not only to be free of pain but also in a "state of exaltation" (Ghosh & Sinha, 2007; Kosambi, 1967). Similarly, some religious fanatics in the Philippines celebrate Easter by flogging themselves, dragging heavy wooden crosses, and crawling on bloody knees. In a recent celebration, nine people had

themselves nailed to crosses in reenactments of the crucifixion. Devotees say that the pain and suffering are a small price to pay to express their faith (Criss, 2019). Figure 8.18 shows examples of culturally sanctioned self-torture.

Figure 8.18 Voluntary Ritualized Torture in Religious Practice.
Cultural values help determine a person's reaction to painful stimulation.

Source: ©Alain Evrard/Photo Researchers

Like other body senses, pain has the somatosensory cortex as its primary projection area. However, pain takes on unique characteristics due to its rich interconnections with the limbic system, particularly the ACC, which in turn is intimately connected with other limbic structures (D. D. Price, 2000). The brain scan in Figure 8.19 shows increased activity in the ACC as well as the somatosensory area during painful heat stimulation. But what evidence is there that activity in the ACC represents the emotional aspect of pain? First of all, in humans and monkeys, some of the neurons respond to the anticipation of pain as well as to painful stimulation (Hutchison, Davis, Lozano, Tasker, & Dostrovsky, 1999; Koyama, Tanaka, & Mikami, 1998). More convincingly, as pain unpleasantness increases, either due to repetitions of the painful stimulus or to hypnotic suggestion, activity increases in the ACC but not in the somatosensory area (D. D. Price, 2000; Rainville, Duncan, Price, Carrier, & Bushnell, 1997). Estimating the pain of others also activates the ACC but not the somatosensory cortex (Jackson, Meltzoff, & Decety, 2005; T. Singer, O'Doherty, Kaube, Dolan, & Frith, 2004). Interestingly, acetaminophen may owe some of its pain-alleviating ability to a dampening of emotion. Compared with control participants receiving a placebo, volunteers who took a typical dose of acetaminophen showed blunted emotional reactions to photos (Durso, Luttrell, & Way, 2015) and rated the physical and emotional pain of others lower (Mischkowski, Crocker, & Way, 2016).



Description

Figure 8.19 PET Scan of Brain During Painful Heat Stimulation.
The bright area near the midline is the cingulate gyrus; the one to the left is in the somatosensory area. The four views were taken simultaneously at different depths in the same brain. (The frontal lobes are at the top of the figure.)

Source: Adapted from Talbot et al., "Multiple Representations of Pain in Human Cerebral Cortex," Science, 251, pp. 1355–1358. Copyright 1991.

? What makes pain an emotional response?

If pain continues, it also recruits activity in prefrontal areas where, presumably, the pain is evaluated and responses to the painful situation are planned (D. D. Price, 2000). The location of pain emotion in separate structures may explain the experience of two groups of patients. In some pain insensitivity disorders, the emotional response is diminished rather than the sensation of pain; the person can recognize painful stimulation but simply is not bothered by it (Melzack, 1973; D. D. Price, 2000). The same is true for people who underwent prefrontal lobotomy back when that surgery was used to manage untreatable pain; when questioned, the patients often said they still felt the "little" pain, but the "big" pain was gone.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- Describe the positive and negative effects of stress, indicating why the effects become negative.
- Discuss the emotional aspects of pain, including the brain structures involved.

BIOLOGICAL ORIGINS OF AGGRESSION

Both motivation and emotion reach a peak during aggression. Aggression can be adaptive, but it also takes many thousands of lives annually and maims countless others physically and emotionally. The systematic slaughter of millions in World War II concentration camps and the terrorist attack that destroyed the World Trade Center

are dramatic examples, but we should not allow such catastrophic events as these to blind us to the more common thread of daily aggression running throughout society.

Aggression is forceful or assertive behavior that is intended to harm or control another. Researchers agree that there is more than one kind of aggression, but they do not agree on what the different kinds are, partly because the forms of aggression differ among species. Animal researchers make a distinction between predatory aggression and affective aggression. **Predatory aggression** occurs when an animal attacks and kills its prey or when a human makes a premeditated, unprovoked attack on another. Predatory aggression is cold and emotionless, whereas **affective aggression** is characterized by its impulsiveness and emotional arousal. Although these terms have been useful in animal research, the terms *instrumental* and *impulsive* seem more descriptive of aggression seen in humans. **Proactive aggression**, or **instrumental aggression**, is unprovoked and emotionless, and it is intended to bring about some gain for the aggressor, for example, to intimidate, dominate, or rob the victim. This type of aggression is often (but not exclusively) seen in people diagnosed with psychopathy and antisocial personality disorder. **Reactive aggression**, or **impulsive aggression**, occurs in response to a threat, real or imagined, and is characterized by heightened emotionality. Frequent and severe episodes of impulsive aggression are characteristic of intermittent explosive disorder.

The Brain's Role in Aggression

Aggression involves the interplay of a network of structures, as you might expect by now. The most important are the amygdala, various parts of the prefrontal cortex, and the hypothalamus, but when emotion is involved, as in the case of provocation, the insula and the ACC are recruited into action as well (Fanning, Keedy, Beman, Lee, & Cocarro, 2017). The amygdala is a central part of the circuit that detects and responds to threats (Coccaro, Sripada, Yanowitch, & Phan, 2011). Stimulation of the amygdala produced anger in aggressive patients, and lesioning of the amygdala improved "intractable aggression" in 33% to 100% of patients (Mpakopoulou, Gatos, Brotis, Paterakis, & Fountas, 2008). Amygdala activity is typically enhanced in people with disorders marked by reactive/impulsive aggression, but individuals with disorders that are typified by emotionless proactive/instrumental aggression—for example, psychopathy and antisocial personality disorder—are more likely to have diminished responses in the amygdala (Coccaro et al., 2011).

You're already familiar with the role of the prefrontal cortex in controlling risky behavior, and it serves a similar function in aggression, particularly with regard to the amygdala. Laboratory studies involving, for example, the opportunity to deliver electric shocks to a nonexistent competitor allow experimental control and the use of brain scans to monitor real-time brain activity. Individuals who are more aggressive in these tasks have consistently been shown to have greater amygdala reactivity to photos of angry faces, reduced activity in the prefrontal cortex (specifically the OFC), and minimal functional connectivity between the prefrontal cortex and the amygdala (Fanning et al., 2017). In a study of convicted murderers, prefrontal activity was essentially normal among proactive murderers, but it was reduced in those whose crimes were impulsive (Raine et al., 1998). And though prefrontal gray matter was reduced by 22% in psychopaths who had been convicted of crimes, those who admitted to crimes but had escaped detection had no deficits (Y. Yang et al., 2005). Thus, although the prefrontal cortex deters most of us from engaging in hostile and aggressive behavior, it fails to do so in others. In still others, it may provide the impulse control and planning ability needed to carry out proactive aggression.

It is no myth that men are more violent than women; a United Nations study found that 96% of murderers worldwide are male (J. Gibbons, 2013). One apparent reason is that men have less gray matter in the prefrontal cortex than women, which in one study accounted for 77% of the men's greater antisocial behavior (Raine, Yang, Narr, & Toga, 2009). Women express guilt and fear of retaliation in relation to aggression, which is open to an interpretation of societal pressure but is also consistent with greater prefrontal activity (Denson, O'Dean, Blake, & Beames, 2018). In laboratory situations, the gender difference decreases when there is provocation and disappears altogether when indirect aggression, such as verbal hostility, is allowed.

The primary neural instigator of aggressive behavior is the hypothalamus; electrical stimulation there reliably induces attack in rats, cats, and monkeys (reviewed in Falkner & Lin, 2014). We know that the hypothalamus is important in human aggression as well, in part because back in the days of psychosurgery, electrical lesions were made in the hypothalamus to treat extreme aggressiveness. Specific areas of the hypothalamus have been identified by using more precisely controllable techniques, such as optogenetic stimulation. Stimulation of the ventrolateral ventromedial hypothalamus causes both male and female mice to attack another animal, and ablation eliminates aggression (Aleyasin, Flanigan, & Russo, 2018; Hashikawa et al., 2017). Stimulation of one group of cells in that area produces defensive aggression against an intruder, while another group initiates unprovoked attack.

Hormones and Neurotransmitters in Aggression

No discussion of the neural bases of aggression is complete without considering the role of hormones and neurotransmitters. When the topic of hormones comes up, we immediately think of testosterone, largely because men are typically more violent than women. So we will look at testosterone first, while acknowledging that it also plays a role in female aggression, and then consider emerging evidence that serotonin and cortisol are equally important as counters to testosterone.

A Further Look:

A Bug That Causes Road Rage?

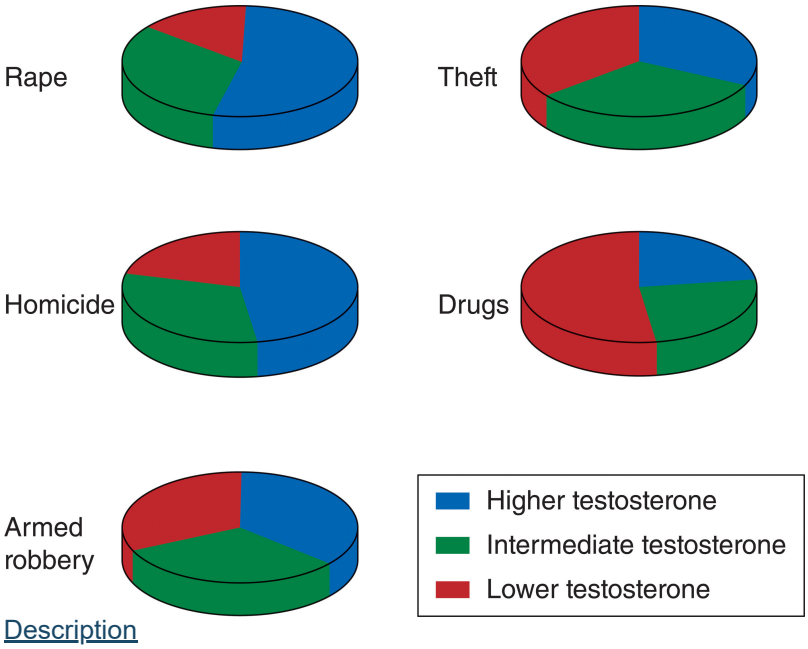
When the protozoan parasite *Toxoplasma gondii* infects animals, it forms cysts in the brain and causes neural damage that changes the host's behavior. Infected animals become risk takers and lose their fear, including failing to avoid predators. Rats and mice, for example, become risk takers and lose their fear of cats; this makes it likely they will get eaten, which means *T. gondii* will end up in the cat's feces, which results in its spread to many new hosts. Concentration of cysts varies among individuals, and attempts to correlate behavioral change with the brain location of infection have been unsuccessful. Instead, the degree of behavioral alteration varies with the number of cysts and the amount of neuroinflammation. Almost one third of the world's human population is infected with *T. gondii*, mostly due to contaminated food and water. Infected individuals are more likely to have car accidents, and infection has been linked to suicide attempts and some cases of psychiatric disorder, such as schizophrenia (Boillat et al., 2019).

Because the cysts are associated with aggression (Cook et al., 2015), Emil Coccaro and his colleagues (2016) at the University of Chicago asked whether the parasite might contribute to intermittent explosive disorder (IED). IED, which affects about 16 million Americans, is exemplified by the impulsive aggression of road rage. Individuals who tested positive for *T. gondii* scored higher on measures of aggression. The rate of infection in individuals diagnosed with IED was 21.8%, compared with 16.7% among those with psychiatric diagnoses and 9.1% of healthy controls. Coccaro said that these results support the view that IED is a brain disorder and not a "disorder of personality."

Testosterone

Testosterone's link with aggression has been long established in both animals and humans. For example, castration of an alpha male rat causes a significant decrease in aggressiveness, along with loss of his dominant position; testosterone replacement prevents these losses (Albert, Walsh, Gorzalka, Siemens, & Louie, 1986). Male monkeys with high testosterone more often engage in aggression that asserts dominance, such as threatening other monkeys or displacing them from their position (Virkkunen, Goldman, & Linnoila, 1996; Virkkunen & Linnoila, 1993). Testosterone levels were higher in male prisoners convicted of violent crimes, such as rape and

murder, and in prisoners rated as tougher by their peers (Figure 8.20; Dabbs, Carr, Frady, & Riad, 1995). In female inmates, testosterone levels were correlated with the violence of their crimes and with aggressive dominance while in prison (Dabbs & Hargrove, 1997). Obviously, it is difficult to observe aggression in humans, so researchers often resort to simulations in the laboratory. For example, testosterone levels were highly correlated with the intensity of shocks college males delivered to a provocative fictitious confederate (Berman, Gladue, & Taylor, 1993).



Description

Figure 8.20 Testosterone Levels of Men Convicted of Various Crimes.
The proportion of men with high testosterone levels compared with other prisoners is greater as the violence of the crime increases.

Source: Based on J. M. Dabbs et al. (1995).

? How is testosterone related to aggression?

Testosterone has significant and sweeping effects in the brain and on behavior. Perhaps the most important outcome of elevated testosterone is reduced functional connectivity between the OFC and the amygdala, leading to poor emotion regulation. Add to that increased motivation, decreased fearfulness, reduced trust (indicated by lower trustworthiness ratings of facial photos), and increased reward sensitivity and risk taking due to dopaminergic activity in the ventral striatum and nucleus accumbens, and you have an individual primed for aggressive action (Eisenegger, Haushofer, & Fehr, 2011; Geniole et al., 2019; Grotzinger et al., 2018).

That said, the relationship between testosterone and aggression is weak and varies from study to study (J. Archer, Graham-Kevan, & Davies, 2005). It turns out that looking at testosterone by itself is not enough. This should come as no surprise, because you have already seen that behavior is a product of the interaction of multiple influences and typically involves a balance between instigators and deterrents. With that thought, we turn our attention to serotonin and cortisol.

Serotonin and Cortisol

Typically, serotonin's role is inhibitory, suppressing motivated behaviors; when serotonin activity is low, appetite increases for food, water, sex, and drugs of abuse (Pihl & Peterson, 1993). Now we will add aggression to the list. A variety of studies

have linked low serotonin with impulsive aggression (R. J. Nelson & Trainor, 2007). Remember in the study of monkeys that those with high testosterone were aggressive; in the same study, the monkeys with low serotonin were impulsive, taking dangerously long leaps among the treetops and allowing occasional aggression to escalate into greater violence (Higley et al., 1996). The most aggressive monkeys had both high testosterone and low serotonin levels. A similar relationship with aggression was seen in violent alcoholic offenders (Virkkunen et al., 1996; Virkkunen & Linnoila, 1993) and in normal males (Kuepper et al., 2010).

Serotonin is important because it plays a crucial role in the inhibition that the prefrontal cortex exerts on aggression. Low serotonin apparently encourages aggression by reducing connectivity of the prefrontal cortex with the amygdala (Passamonti et al., 2012). Loss of typical prefrontal restraint leaves the amygdala free to overreact to threat. Antidepressants that block reuptake of serotonin at the synapses (selective serotonin reuptake inhibitors, or SSRIs) increase serotonin levels and reduce aggressive behavior. They do this by normalizing prefrontal responses to social threat and reducing typically heightened amygdala responses (Coccaro, Fanning, Phan, & Lee, 2015).

Like serotonin, cortisol also inhibits aggression. Male prisoners with low cortisol had high levels of aggression and were more likely to be diagnosed as psychopathic, meaning that their aggression was calculating and unemotional (Cima, Smeets, & Jelicic, 2008). Numerous studies have linked aggression to a combination of high testosterone and low cortisol (see Montoya, Terburg, Bos, & van Honk, 2012, for references), even in girls (Platje et al., 2015). Neither testosterone's nor cortisol's effect is limited to aggression; high testosterone combined with low cortisol predicted higher numbers of subordinates assigned to male executives, a measure of corporate success (Sherman, Lerner, Josephs, Renshon, & Gross, 2015).

We are now beginning to see a counterbalanced system of opposed hormones and transmitters, just as we did with the neural structures involved in aggression. As you know, serotonin controls aggression through its inhibitory influence on the amygdala, and cortisol exerts its inhibition by increasing expression of genes in the amygdala to facilitate avoidance, whereas testosterone upregulates other genes there to facilitate aggression (Montoya et al., 2012). According to one hypothesis, these three factors work in concert to determine both whether and how aggression will occur (Montoya et al., 2012). A high testosterone-to-cortisol ratio predisposes to aggression; low serotonin then predisposes to impulsive aggression, whereas high serotonin, if it does not suppress the behavior, channels it into planned, instrumental aggression.

Two other transmitters are worth noting because they will show up in the next section. Dopamine levels increase during aggression in animals, and antidopaminergic drugs alleviate aggression in some psychiatric patients (Narvaes & de Almeida, 2014); this is consistent with the association of aggression with increased reward sensitivity and risk-taking mentioned earlier. Gamma-aminobutyric acid (GABA) is, of course, the main inhibitory neurotransmitter in mammalian brains, and most studies report an inhibitory effect on aggression, but there have been contradictory results, possibly because its influence also depends on the other players.

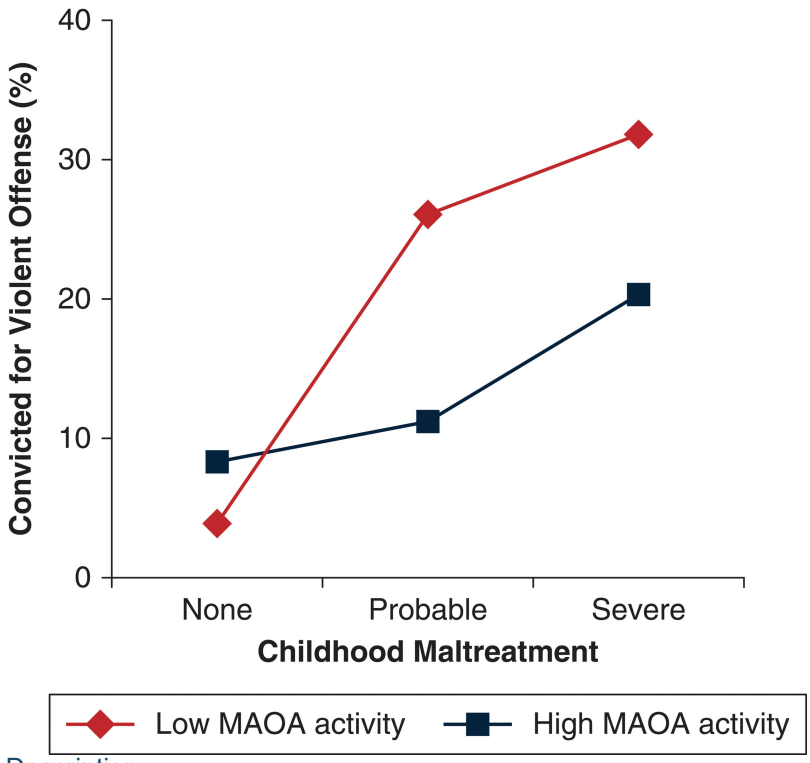
Heredity and Environment

A review of 40 twin studies concluded that about 50% of the variability in aggressive behavior can be accounted for by genes (Veroude et al., 2016). Identifying these genes is difficult because of the inherent difficulties in studying aggression, the large number of genes involved, and the fact that different genes are involved at different stages of life. The latter was exemplified in a study that found one set of genes accounting for the high level of peer aggression during the ages of 2 to 4, and another as the children learned to control aggression as cognitive resources and impulse control improved (Paquin et al., 2017). A review of available data identified 40 of the most influential genes. They fell into three functional groups, which were related to development and function of the central nervous system, communication within cells, and cellular function and maintenance (Zhang-James et al., 2019).

The specific genes identified most often have functions in serotonin and dopamine transmission (Fernàndez-Castillo & Cormand, 2016; Veroude et al., 2016). Examples are the serotonin transporter gene, *5HTT* (also known as *SLC6A4*), and the dopamine transporter gene, *DAT1* (or *SLC6A4*); transporter genes encode proteins that return the neurotransmitter to the presynaptic neuron after the neuron fires. The *MAOA* gene encodes monoamine oxidase A (MAOA), an enzyme that degrades serotonin, dopamine, and norepinephrine. Deficiencies in MAOA activity have been associated with impulsive aggression in numerous studies. The short alleles of the *MAOA* gene, known collectively as *MAOA-L*, result in low levels of monoamine oxidase; their association with impulsive aggression has earned them the nickname "warrior genes." And considering the role of testosterone in aggression, it is not surprising that some studies have also identified the androgen receptor gene, *AR*, as important; two alleles may distinguish between impulsive and instrumental aggression (Waltes, Chiocchetti, & Freitag, 2016).

But what are the environmental influences that account for the other 50% of variation in aggression? Research has suggested a host of possibilities, including childhood physical or sexual abuse, family adversity, low socioeconomic status, pre-adulthood cannabis consumption or alcohol abuse, and even living in a big city (Mitjans et al., 2019; Tuvblad & Baker, 2011). Unfortunately, these studies don't allow us to rule out the possibility that the presence of these factors results from genetic characteristics of the parents, which are often shared with the individual. Marina Mitjans and her colleagues did take a step in the right direction when they determined that the high-risk individuals in their study had a higher level of epigenetic changes. But at the same time, we can't be sure whether those changes were induced by the childhood experiences or resulted from the stress and conflict of years of engaging in aggressive behavior.

This is a good time to remind you that genes and environment don't operate in isolation but interact with each other. A good example is that whether childhood adversity results in adult aggressiveness depends in part on the level of *MAOA* gene activity. In a study that followed more than 1,000 children to the age of 26, those who suffered maltreatment as children were more likely to be incarcerated for violent crimes only if they also had the *MAOA-LPR* form of the gene, which results in low monoamine oxidase levels (Figure 8.21; Caspi et al., 2002). Although these individuals comprised only 12% of the total group, they accounted for 44% of the violent convictions.



Description

Figure 8.21 Genetic Influence on Violent Behavior in Victims of Childhood Maltreatment.
Low MAOA activity due to the *MAOA-L* allele, coupled with childhood maltreatment, results in increased violence.

Source: Based on data from "Role of Genotype in the Cycle of Violence in Maltreated Children," by A. Caspi et al., 2002, *Science, 292*, p. 852.

Violent behavior has been viewed in the past almost exclusively as a social problem. But authorities and the community alike are increasingly recognizing that we must combine environmental explanations with biological understanding if we are to deal with violence effectively. That is the approach of neurocriminology, which is the subject of A Further Look.

A Further Look:

Neurocriminology, Responsibility, and the Law

Adrian Raine

Source: Lawrence K. Ho/Los Angeles Times/Getty Images

In 1999, Donta Page robbed a young Denver woman and then raped and killed her. During the trial, British psychologist Adrian Raine testified that Page had a “perfect storm” of predisposing factors: a family history of mental illness; a distinct lack of activation in the prefrontal cortex (Glenn & Raine, 2014); and a childhood of poor nutrition, lead exposure, parental neglect, repeated physical and sexual abuse, and head injuries (Raine, 2013). As a result of Raine’s testimony, Page received a life sentence rather than the death penalty.

Raine (who is cited frequently in this chapter) is a pioneer in the emerging field of neurocriminology, which uses neuroscience to understand and prevent criminal behavior. He raises the question of whether we should hold criminals like Page to the same level of accountability we expect of other people. For emphasis, he points out that violence in the United States has closely tracked the rise and fall of lead in gasoline, which can statistically account for 91% of the changes in violence from the 1970s to the present (“Criminologist Believes Violent Behavior…,” 2013).

In spite of Page’s impairments, his crime didn’t have to happen. Earlier in 1999, he had come before the parole board while serving time for robbery. Had Raine been called on to testify then, he would have told the board that Page was at high risk for violence and should not be returned to society (Raine, 2013). Instead, Page was set free after serving 4 years of a 20-year term, and he murdered the young woman just 4 months later. Applying the expertise of neurocriminology earlier in a criminal’s career could reduce later violence through treatment and more enlightened decisions about sentencing and parole. Obstacles standing in the way of this approach are the lack of research funding and outmoded attitudes of officials and the public when it comes to brain disorders, mental illness, and responsibility. A positive outcome of the December 2012 Sandy Hook school shooting is that the parents of one victim, 6-year-old Avielle Richman, established the Avielle Foundation to foster more constructive attitudes and to encourage neuroscience research on the causes of violence (T. Smith, 2013).

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- Make a table with the following column headings: Prefrontal Cortex, Amygdala, Testosterone, Serotonin, and Cortisol. Under each heading, indicate the structure's or hormone's contribution to aggression (including interactions with others in the table).
- Write your own theory of what causes impulsive and instrumental aggression.
- Do you think *T. gondii* is intentionally ensuring its own success when it induces a rat to get itself eaten? Explain from an evolutionary perspective.

IN PERSPECTIVE

Emotion has been difficult for neuroscientists to get a handle on because it is so complex physiologically and because so much of emotion is a subjective, private experience. With improved research strategies and new technologies such as PET scans, old questions about the role of brain structures are finally yielding to research. A good example is the ability to separate the emotion of pain from its sensory aspects at the neural level. On another front, research has confirmed the influence of emotion on health, a topic that was practically relegated to fringe psychology not too long ago.

We have focused mostly on the negative aspects of emotion because they have received the most attention from researchers and we know more about them. Stress, pain, anger, and aggression are viewed as some of our greatest burdens, but they are permanently etched into our behavior because they helped ensure our ancestors' survival. Because they are part of our biology, we can sometimes treat these problems with medication and will likely be able to use genetic interventions in the future. But society also needs to ask itself whether fewer students would show up at school with a weapon if we started thinking of it as an environmental problem, or if terrorism could be reduced through better international understanding, as well as whether we need to appreciate the role of hormones, genes, and the brain when judging the accountability of a murderer. In the meantime, if you find thoughts about the negative aspects of emotion a bit depressing, you might want to take a short break while you hold your pen between your teeth; brightening your corner of the world is a good place to start.

Chapter Summary

Emotion and the Nervous System

- The autonomic nervous system increases bodily arousal during an emotional event and decreases it afterward.
- The James-Lange and cognitive theories differ as to the role of bodily feedback in emotional experience. There is evidence that bodily feedback, especially from facial expressions, contributes to emotions; also, mimicking other people's expressions may help us understand others' emotions.
- The limbic system is a network of several structures that have functions in emotion.
- The amygdala has a variety of functions, but its role in fear has received the most attention. Rats and humans with damage to both amygdalas lack fear and often fail to act in their own best interest.
- The prefrontal cortex combines emotional input with other information to make decisions. People with prefrontal cortex damage have trouble following moral and social rules, and they have impaired ability to learn from the consequences of their behavior.

Stress, Immunity, and Health

- Stress is initially adaptive, mobilizing the body for action and increasing immune system activity.
- Prolonged stress interferes with mental, physical, and emotional functioning; compromises the immune system; and even damages the brain.
- Social support, personality, and attitudes are related to immune functioning and health. However, instead of influencing immune functioning, these social and personality factors may be indicators of the individual's physiological functioning.
- Pain is also an adaptive response; it informs us of danger to the body, and the emotion that accompanies it motivates us to take action.

Biological Origins of Aggression

- Researchers usually distinguish two types of aggression in animals, predatory and affective; in humans, the two types are known as proactive or instrumental and reactive or impulsive.
- Aggression arises from the hypothalamus and, at least in the case of impulsive aggression, from the amygdala. The prefrontal cortex typically inhibits aggression, but in aggressive individuals, its role in planning and impulse control may distinguish proactive from reactive aggression.
- High testosterone is involved in both male and female aggression.
- Serotonin and cortisol inhibit aggression. Low serotonin in combination with high testosterone predisposes a person to reactive, impulsive aggression, while low

cortisol makes calculating, proactive aggression more likely. There is also some evidence for involvement of dopamine and gamma-aminobutyric acid.

- Heritability of aggressive behavior is about 50%, with most of the remainder due to nonshared environmental influences.
- Genes that contribute to aggression are related to central nervous system development and function, communication within cells, and cellular function and maintenance. These include several involved in neuronal and forebrain development. Specific genes include serotonin and dopamine transporter genes, the *MAOA-L* alleles, and the androgen receptor gene.
- Several environmental associations have been identified, but determining causal relationship is difficult. Environmental associations include childhood abuse, family adversity, low socioeconomic status, pre-adulthood alcohol and cannabis use, and even living in a big city. Gene-environment interaction is illustrated by the finding that *MAOA-LPR* allele contributed to aggression only in individuals who had been abused as children.

Study Resources

For Further Thought

- Do you think we rely more on bodily feedback or the stimulus situation in identifying emotions? Why?
- Stress and pain involve considerable suffering, but they are necessary. Explain. What differentiates between good and bad stress and pain?
- You are an adviser to a government official charged with reducing aggression in your country. From what you have learned in this chapter, what would you recommend?
- The legal plea of “not guilty by reason of insanity” has historically required that the defendant did not *know* right from wrong—as evidenced, for example, by the defendant’s failure to flee or try to conceal the crime. Critique this standard in terms of what you know about controlling behavior.

Test Your Understanding

1. Discuss the James-Lange and cognitive theories, including evidence for each theory.
2. Explain the roles of the amygdala and the prefrontal cortex in guiding our decisions and behavior.
3. Describe the role the brain plays in animal and human aggression, including structures and their functions.

Select the best answer:

1. The James-Lange theory and the cognitive theory disagree on whether
    1. specific brain centers are involved in specific emotions.
    2. there is any biological involvement in human emotions.
    3. bodily feedback determines which emotion is felt.
    4. individuals can judge their emotions accurately.
2. Some people with brain damage do not seem to learn from the consequences of their behavior and must have supervised care. Based on the likely location of their damage, you would expect that they would be deficient in
    1. sadness.
    2. joy.

3. fear.
4. motivation.

3. Hypothalamus-pituitary-adrenal axis activity is a chain of events ending with the release of
    1. norepinephrine and epinephrine.
    2. cortisol.
    3. corticotropic-releasing hormone.
    4. adrenocorticotropic hormone.
4. Stress can
    1. reduce immune system function.
    2. impair health.
    3. mobilize the immune system.
    4. a and b
    5. a, b, and c
5. Long-term exposure to cortisol may affect memory by
    1. reducing blood flow to the brain.
    2. destroying neurons in the hippocampus.
    3. inhibiting neurons.
    4. redirecting energy resources to the internal organs.
6. Prolonged stress alters the
    1. amygdala.
    2. prefrontal cortex.
    3. hippocampus.
    4. a and b
    5. a, b, and c
7. Indications are that if pain did not have an emotional component, we would probably
    1. be deficient in avoiding harm.
    2. avoid harm by using learning and reasoning.
    3. be more aggressive.
    4. generally lead happier lives.
8. A structure described in the text as being involved in both aggression and flight is the
    1. amygdala.
    2. anterior cingulate cortex.
    3. lateral hypothalamus.
    4. periaqueductal gray.
9. According to research, you would have your best chance of showing that testosterone increases aggression in humans if you injected testosterone into people
    1. who had been abused during childhood.
    2. with high cortisol.
    3. with high activity in the prefrontal cortex.
    4. lacking *MAOA-L* alleles.
10. During aggression, activity in the hypothalamus, amygdala, and prefrontal cortex would likely be _____, respectively.
    1. high, high, high
    2. low, high, high
    3. high, low, high
    4. high, high, low

Answers:

1. c, 2. c, 3. b, 4. e, 5. b, 6. e, 7. a, 8. d, 9. a, 10. d.

For Further Reading

1. *Descartes' Error*, by Antonio Damasio (Penguin Books, 2005), is a timeless classic that develops the premise that our rational decision making is largely dependent on input from emotions.
2. *Behave: The Biology of Humans at Our Best and Worst* (Penguin Group, 2017) is Robert Sapolsky's highly acclaimed latest treatment of violence, aggression, and competition.

3. “Empathy Overkill,” by Helen Thomson (*New Scientist*, March 13, 2010, 43–45), describes research with people with “mirror synesthesia,” who intensely feel what they see others experiencing, and people with echopraxia, who greatly exaggerate the action mimicking that the rest of us engage in subtly.
4. *The Sickening Mind*, by Paul Martin (Flamingo, 2016), is about the interplay of emotion, stress, and immunity in shaping our health.
5. *Personality and Disease: Scientific Proof vs. Wishful Thinking* (Academic Press, 2018) is Christoffer Johansen’s compilation of years of research from the fields of psychology, behavioral health, psychoneuroimmunology, oncology, and epidemiology on the relationship between personality and health.
6. In *Mama’s Last Hug: Animal Emotions and What They Tell Us About Ourselves* (W. W. Norton, 2019), Yerkes Lab primatologist Frans de Waal, one of *Time* magazine’s 100 Most Influential People, marshals his four decades of research to make the case that it’s likely that no emotion is uniquely human.
7. *The Better Angels of Our Nature: Why Violence Has Declined*, by Steven Pinker (Penguin Books, 2012), argues that in spite of what we see in the news, violence is declining worldwide, and we may be living in the most peaceful era of human existence. Pinker attributes this in part to increasing empathy, as a result of literacy, travel, and a broader worldview.
8. *The Anatomy of Violence: The Biological Roots of Crime*, by Adrian Raine (Pantheon, 2013), describes his work and that of others over the past three decades teasing out the biological causes of crime and what can be done, while establishing the new field of neurocriminology.

Key Terms

affective aggression 260

aggression 260

amygdala 246

anterior cingulate cortex (ACC) 249

autoimmune disorder 253

B cell 252

cognitive theory 243

congenital insensitivity to pain 258

cortisol 251

emotion 242

hypothalamus-pituitary-adrenal axis 251

immune system 252

impulsive aggression 260

instrumental aggression 260

James-Lange theory 243

leukocytes 252

limbic system 245

macrophage 252

microglia 252

mirror neurons 244

natural killer cell 252

predatory aggression 260

proactive aggression 260

reactive aggression 260

skin conductance response (SCR) 249

stress 251

sudden cardiac death 254

T cell 252

Descriptions of Images and Figures

Back to Figure

The data from the illustration are tabulated below.

Back to Figure

1. Botox: A photo shows smooth forehead of a woman.
2. A brain scan shows an arrow pointing toward a small area of activation of the amygdala.
3. Normal: A photo shows a person drawing their eyebrows together.
4. A brain scan shows an arrow pointing toward a large area of activation of the amygdala.

Back to Figure

In the brain, the cingulate gyrus surrounds the fornix. The fornix and parahippocampal gyrus surround the thalamus, hypothalamus, mammillary body, hippocampus, and amygdala. Septal nuclei is located inferior to the thalamus.

Back to Figure

The illustration shows longitudinal fissure on the dorsal side surrounded by cingulate cortex, B N S T located inferior to the ventricles, amygdala on the ventral side, and lateral fissure on the sides surrounded by insular cortex.

Back to Figure

1. The ventral surface of the brain shows orbitofrontal cortex along the lateral sides of the prefrontal cortex and ventromedial cortex along the medial side of the prefrontal cortex, on either side of the longitudinal fissure.
2. The ventral surface of the brain shows a dashed line across the middle of the prefrontal cortex. Brain damage corresponding to number 1 is along the ventromedial cortex and along the medial regions of orbitofrontal cortex. Brain damage corresponding to numbers 2, 3, and 4 is along the edges of orbitofrontal and ventromedial cortices on the left side of the brain.
3. A cross section of the prefrontal cortex along the dashed line shows most of the damaged areas on the ventral surface of the brain.

Back to Figure

In both graphs, the horizontal axis lists controls and patients.

a. The graph is titled, choices from card decks. The vertical axis is labeled Average cards selected in last 20 choices, and ranges from 0 to 20, in increments of 5. The approximate data from the graph are tabulated below.

b. The graph is titled, choices from card decks. The vertical axis is labeled Average size of anticipatory S C Rs, and ranges from 0 to 0.20, in increments of 0.5. The approximate data from the graph are tabulated below.
Back to Figure

The pathways are as follows.

1. Amygdala in the right temporal lobe activates hypothalamus.
2. Hypothalamus activates the adrenal medulla surrounded by adrenal cortex.
3. Epinephrine and norepinephrine is released by adrenal medulla.
4. C R H secreted by the hypothalamus.
5. A C T H released by the pituitary gland is transported to the adrenal cortex.
6. The cortex releases cortisol.
7. Cortisol from the adrenal cortex is transported to the pituitary gland and hypothalamus.

Pathways numbered 1 and 2 are neural pathways, and pathways numbered 3 through 7 are circulatory pathways.

Back to Figure

The horizontal axis is labeled stress index. The vertical axis is labeled subjects with cold in percentage, and ranges from 20 to 50 in increments of 5. The approximate data from the graph are tabulated below.

Back to Figure

The horizontal axis is labeled January 1994, and ranges from 10 to 23 in unit increments. The vertical axis is labeled Number of deaths, and ranges from 0 to 30 in increments of 10. The approximate data from the graph are tabulated below.

Back to Figure

The horizontal axis lists the conditions in mice. The vertical axis ranges from 0 to 250 in increments of 50. The approximate data from the graph are tabulated below.

Back to Figure

The first scan is labeled D V positive 64 and shows activation corresponding to high t-value.

The second scan is labeled D V positive 47 and shows activation corresponding to high t-value.

The first scan is labeled D V positive 61 and shows activation corresponding to moderate t-value.

The second scan is labeled D V positive 43 and shows activation corresponding to low t-value.

Back to Figure

The data from the charts are tabulated below.

Back to Figure

The horizontal axis is labeled childhood maltreatment, and lists none, probable, and severe. The vertical axis is labeled Convicted for violent offense in percentage, and ranges from 0 to 40 in increments of 10. The approximate data from the graph are tabulated below.

PART III INTERACTING WITH THE WORLD

Chapter 9. Hearing and Language

Chapter 10. Vision and Visual Perception

Chapter 11. The Body Senses and Movement

9 HEARING AND LANGUAGE

© Photo courtesy of Eric Schrader.

Hearing

- The Adequate Stimulus for Hearing
- The Auditory Mechanism
- Frequency Analysis
- Restoring Hearing

A Further Look | Beyond Cochlear Implants

- Analyzing Complex Sounds
- Locating Sounds

A Further Look | I Hear a Tree Over There

Concept Check

Language

Broca's Area

Wernicke's Area

The Wernicke-Geschwind Model

Reading, Writing, and Their Impairments

Recovery From Aphasia and Lateralization of Language

A Language-Generating Mechanism?

Language in Nonhuman Animals

Neural and Genetic Antecedents

A Further Look | What Do the Gestures of Apes and Humans Have in Common?

Concept Check

In Perspective

Chapter Summary

Study Resources

After reading this chapter, you will be able to

9.1 Summarize how the nervous system processes sound stimuli.

9.2 Identify the brain structures involved in hearing.

9.3 Describe the role of specific brain structures in language ability.

9.4 Explain how lateralization is important to the brain organization of language processing.

9.5 Identify the brain regions impaired in specific language disorders.

9.6 Contrast the communication abilities of other animals with human language.

The movie *A Quiet Place* follows a family as they attempt to survive invading aliens. Blind but with highly sensitive hearing, the aliens stalk and kill humans by detecting the slightest sound or softest whisper, requiring the family to live in silence. Regan, the older daughter, is deaf; she finds herself in peril multiple times because her cochlear implant is malfunctioning, so she cannot recognize when she or someone else makes a sound that could attract the aliens.

The character is played by teenage Millicent Simmonds (Figure 9.1), herself deaf from the age of 1 year after her hearing was damaged by an overdose of medication. She has thrived, relying on American Sign Language (ASL) and a cochlear implant, which bypasses the damaged receptors in her ear and stimulates the auditory nerves directly. She began acting in the drama club of the Jean Massieu School of the Deaf and continued in her local public school. At the age of 12, she was cast in a major role in the film *Wonderstruck*, and *A Quiet Place* followed the next year. Between the

two films, she received 10 award nominations, demonstrating that a person can excel in spite of a serious disability.

Description

Figure 9.1 Millicent Simmonds.

Michael Loccisano/Getty Images

With the topics of hearing and language, we begin the discussion of how we carry on transactions with the world. This communication involves acquiring information through the senses, processing the sensory information, communicating through language, moving about in the world, and acting on the world. We have already touched on the senses of taste, smell, and pain in the context of hunger, sexual behavior, and emotion. Before we explore additional sensory capabilities, we need to establish some basic concepts.

First, every sensory system must have a specialized receptor. A **receptor** is a cell, often a specialized neuron, that is suited by its structure to respond to a specific form

of energy, such as the mechanical vibration of sound. A receptor's function is to convert that energy into a corresponding pattern of neural responses. You will see examples of two types of receptors in this and the next chapter, but receptors come in a wide array of forms to carry out their functions.

? How is a stimulus translated into information the brain can use?

For a receptor to do its job, there must also be an adequate stimulus. An **adequate stimulus** is the energy form for which the receptor is specialized. Due to the imperfect specialization of receptors, other stimuli will often produce responses as well. For example, if you apply gentle pressure to the side of your eyeball (through the closed lid), you will see a ring of light caused by mechanically stimulating normally light-sensitive receptors inside your eye.

? What is the difference between sensation and perception?

You will remember from Chapter 3 that according to Müller's doctrine of specific nerve energies, the neural mechanism determines the kind of sensory experience you will have. A sensory system will register its peculiar type of experience even if the stimulus is inappropriate. So when the neurosurgeon stimulates the auditory cortex, the patient hears a buzzing sound or even voices or music, and when your skateboard shoots out from under you and your head hits the pavement, you really do see "stars." You will learn in this and the next two chapters that it is the intensity and pattern of the stimulation—that is, the amplitude and timing of neural impulses—that makes sensory information meaningful.

Most people consider audition and vision the two most important senses. As a result, there has been more research on these two senses than on the others, and therefore we know more about them, so we will give them the most attention. Because audition is a more mechanical sensory process than vision, it is a good place to begin our formal discussion of **sensation**, the acquisition of sensory information, and **perception**, the interpretation of sensory information.

HEARING

The fact that the auditory mechanism is less complex does not mean that hearing is a simple matter. The **cochlea**, where the auditory stimulus is converted into neural impulses, contains thousands of moving parts. Our range of sensitivity to intensity, from the softest sound we can hear to the point where sound becomes painful, is 10 trillion to 1. Our ability to hear low-intensity sounds is limited more by interference from the sound of blood coursing through veins and arteries than by the auditory mechanism itself. In addition, we can hear frequencies ranging from about 20 hertz (Hz, cycles per second) up to about 20000 Hz, and we can detect a difference in frequencies of only 2 or 3 Hz. To give you some idea of what these frequencies relate to in real life, the piano—the most versatile of musical instruments—has a range of about 27 to 4000 Hz. Upper ranges are more impressive for some animals: 60000 Hz (60 kHz) for dogs, 79 kHz for cats, and an astonishing 300 kHz in a species of moth (Moir, Jackson, & Windmill, 2013)—15 times higher than for humans.

The Adequate Stimulus for Hearing

The adequate stimulus for audition is vibration in a conducting medium. For humans, the conducting medium is normally air, but we can also hear vibrations in water, as well as those conducted through our skulls. The air is set to vibrating by the vibration of the sound source—a person's vocal cords, a bell that has been struck, or a speaker. As the sound source vibrates, it alternately compresses and decompresses the air (Figure 9.2).

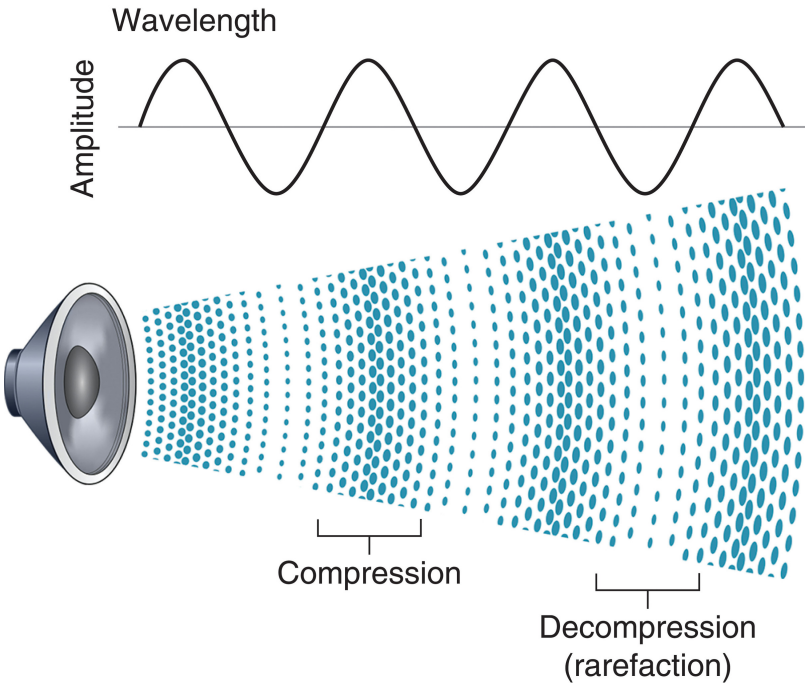
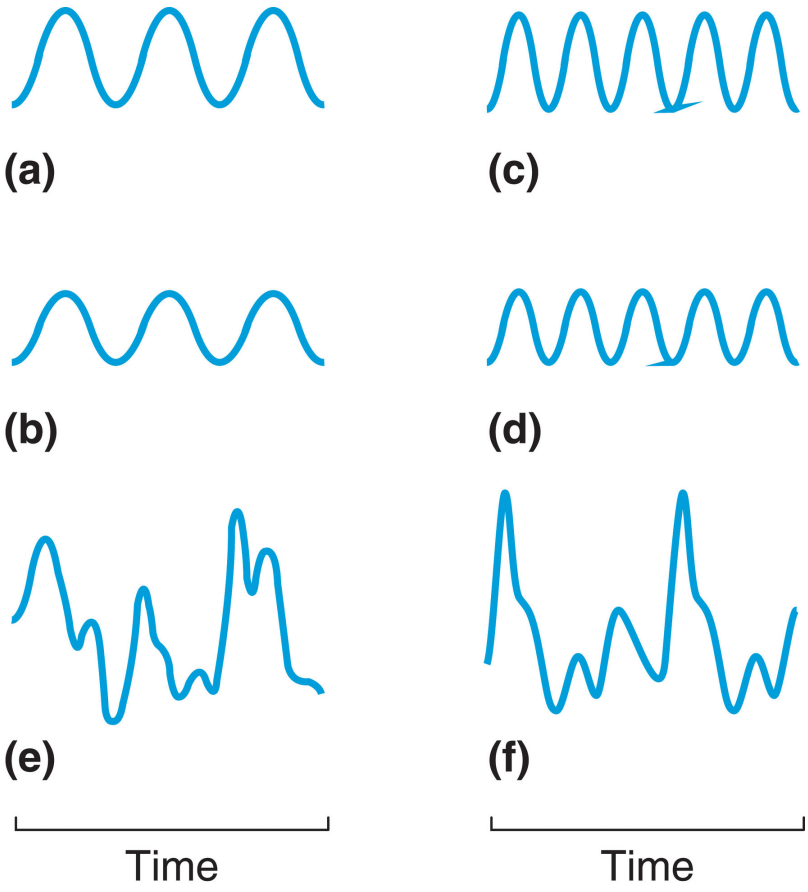


Figure 9.2 Alternating Compression and Decompression of Air by a Sound Source. The speaker's diaphragm moves in and out, alternately compressing and decompressing the surrounding air. The dark areas represent high pressure (a denser concentration of air molecules), and the light areas represent low pressure.

Source: From *Sensation and Perception*, 5th ed., by Goldstein, 1999. Reprinted with permission of Wadsworth, a division of Thomson Learning.

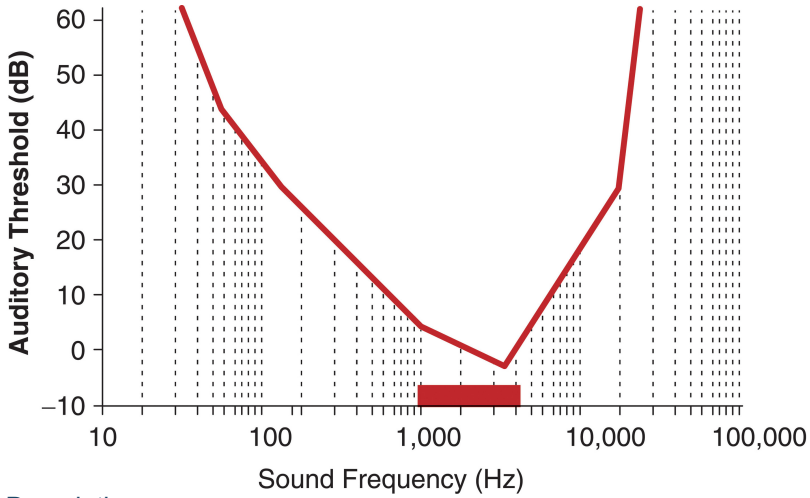
If we used a microphone to convert a sound to an electrical signal, we could display the signal on a computer, like the one we used to measure the action potential in Chapter 2; the oscillations of the sound wave would form a graph of compressions and decompressions, and we could see what the sound "looks like." In Figure 9.3, the up-and-down squiggles represent the increasing and decreasing pressure of different sounds (over a brief fraction of a second). One way sounds differ is in frequency. **Frequency** refers to the number of cycles or waves of alternating compression and decompression of the vibrating medium per second (expressed in Hz). Figure 9.3a and 9.3b have the same frequency—indicated by the number of waves in the same time—so we would hear these two sounds as the same, or nearly the same, pitch. Figure 9.3c and 9.3d would also sound about the same as each other, but higher in pitch than Figure 9.3a and 9.3b. **Pitch** is our psychological perception of the frequency of a sound—more waves per second correspond to higher perceived pitch. We said "about the same," because the perception of pitch is affected somewhat by the intensity of the sound.



Description

Figure 9.3 Examples of Pure and Complex Sounds.
(a) and (b) are pure tones of the same frequency but different amplitudes, as are (c) and (d). (a) and (c) have the same amplitudes but different frequencies, as do (b) and (d). Both (e) and (f) are complex sounds—noise and a clarinet note, respectively.

Sounds also differ from each other in intensity and loudness. **Intensity** is the term for the physical energy in a sound; **loudness** is the term for our perception of a sound's intensity. Intensity and loudness are not the same, because we are more sensitive to some frequencies than others; as you can see in Figure 9.4, our hearing is markedly better between 1000 and 4000 Hz, the range within which most conversation occurs (Figure 9.4). In Figure 9.3, *a* has a greater amplitude (height of the wave) and therefore greater intensity than *b*; a will also sound louder than *b*. Figure 9.3a and 9.3c are equal in intensity, but they might not sound equally loud, due to their difference in frequency. Sound intensity is usually measured as the sound pressure level (the pressure exerted by the sound wave) using a microphone and an electronic meter. Measurement is in decibels (dB); this is a logarithmic scale, which is suited to accommodating both our incredibly wide range of hearing and our greater sensitivity at low intensities. For example, normal conversation occurs at around 60 dB, while the sound of a military jet, at 10 trillion times greater than threshold, is only about 140 dB. Loudness is measured based on equivalence to a 1000-Hz tone; a tone that sounds as loud as the 1-kHz tone at 60 dB has a loudness of 60 phons. The sone scale is similar, but with 1 sone set at 40 phons. Because the physical stimulus and the psychological experience are not always perfectly related, we need to use the terms *intensity* versus *loudness* and *frequency* versus *pitch* carefully.



Description

Figure 9.4 Human Audiogram.
Humans have the best sensitivity between 1000 and 4000 Hz, where the frequencies of language are found (red bar on bottom).

Source: Adapted from: "On Minimum Audible Fields," by L. J. Sivian and S. D. White, 1933, *Journal of the Acoustical Society of America*, 4, 288–321.

The sounds we hear can also be classified as either pure tones or complex sounds. A pure tone, generated, for example, by striking a tuning fork, would produce a tracing on an oscilloscope that looks like one of the graphs in Figure 9.3a–d. Notice that these four waveforms are a very regular shape, called a sine wave. Each is a **pure tone**, with only one frequency. A **complex sound**, which mixes several frequencies, is represented in Figure 9.3e and 9.3f. The random combination of frequencies in Figure 9.3e would be perceived as "noise." Depending on the combination of frequencies and their amplitudes, a complex sound might seem musical, like the last waveform in Figure 9.3f, which was produced by a clarinet. The two waveforms may not look very different to you, but they would certainly sound different. Although what is considered *pleasantly* musical depends on experience and culture (and one's age!), we would recognize even the most foreign music as music.

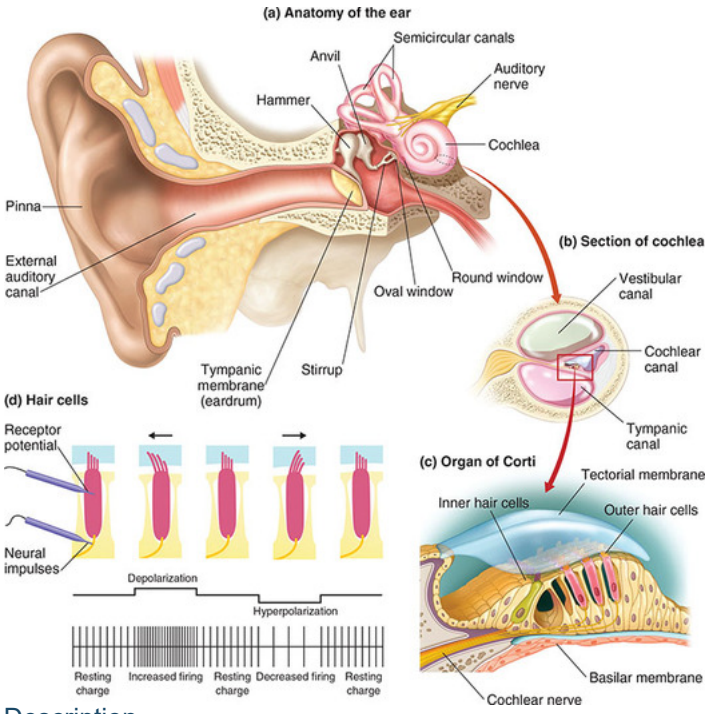
The Auditory Mechanism

To hear, we must get information about the sound to the auditory cortex. This requires a series of events, including sound reception, amplification, and conversion into neural impulses that the brain can use. Before we get to the functional aspects of encoding sound and how we extract meaningful information from a complex auditory environment, we will first begin with a survey of the structures of brain areas involved in processing sound.

The Outer and Middle Ear

The term *ear* refers generally to all the structures shown in Figure 9.5. The flap that graces the side of your head is called the outer ear or **pinna**. The outer ear filters the sound and then amplifies it slightly by funneling it from the larger area of the pinna into the smaller area of the auditory canal. It also selects for sounds in front; this makes it easier to focus on a sound, such as the conversation you're having, while excluding irrelevant sounds around you. Dogs and cats have muscles that enable them to turn their ears toward a sound that is not directly in front of them; you may be able to wiggle your ears a bit by twitching your scalp muscles, but you must turn your head to orient toward a sound. A unique aspect of your pinna is that its unique shape and filtering properties allow you to map sound objects in the world around you—if

you wear earbuds that bypass your pinna, sound objects appear to be located within your own head rather than out in the world.



Description

Figure 9.5 Structures of the Outer, Middle, and Inner Ear.
(a) The outer ear—pinna and auditory canal (brown); the middle ear—tympanic membrane and three ossicles (red); and the inner ear—the cochlea and auditory nerve (pink). (b) A section of the cochlea, showing the three fluid-filled canals. (c) Schematic showing the organ of Corti, including three rows of outer hair cells (pink) and one row of inner hair cells (green). (d) How hair cell movements translate into auditory nerve action potentials. When hair cells bend to the left, potassium (K) inflow causes hair cells to increase their firing rates. When hair cells bend to the right, K outflow causes hair cells to decrease their firing rates.

Source: (d) Koeppen & Stanton: *Berne & Levy Physiology* (6th Edition), Copyright 2008 by Mosby/Elsevier Inc.

The separation between the outer and middle ear is the eardrum or **tympanic membrane**, a very thin membrane stretched across the end of the auditory canal; its vibrations transmit sound energy to the three middle ear bones (or ossicles). A muscle called the *tensor tympani* can stretch the eardrum tighter or loosen it to adjust the sensitivity to changing sound levels. You can hear it contract when you yawn. The second part of the middle ear is the **ossicles**, tiny bones that operate in lever fashion to transfer vibrations from the tympanic membrane to the cochlea. The *malleus*, *incus*, and *stapes* are named for their shapes, as you can see from their English equivalents *hammer*, *anvil*, and *stirrup*. By concentrating the energy collected from the larger tympanic membrane onto the much smaller base of the stirrup, which rests on the end of the cochlea, the ossicles amplify the sound approximately 30-fold. The amplification is more than enough to compensate for the loss of energy as the vibration passes from air to the denser liquid inside the cochlea. The ossicles are not passive players in the auditory process: The muscles attached to them tighten the joints to increase sensitivity to soft sounds and loosen the connections to dampen loud sounds. In addition to these sound-related structures, the middle ear also contains the **Eustachian tube**, connecting the middle ear to the back of your mouth, which equalizes the air pressure of the middle ear with the outside world. Pressure differences between the middle ear and the outside world put pressure on the tympanic membrane, which hurts. Therefore, your ears hurt when you dive deep in a

pool or climb up a mountain; yawning or chewing gum can open a blocked Eustachian tube, causing a “pop” as the pressure suddenly equalizes and the tympanic membrane returns to its normal shape.

The Inner Ear

Just like a membrane separates the outer and middle ears, membranes separate the air-filled middle and the fluid-filled inner ear (called the *oval* and *round windows*). You can also see the parts of the inner ear in Figure 9.5. The snail-shaped structure is the cochlea, where the ear’s sound-analyzing structures are located. You can see from the cochlea’s shape where it got its name, which means “land snail” in Latin. Figure 9.5a shows a more highly magnified view. It is a tube that is about 35 millimeters (mm) long in humans and coiled two and a half times. This tube is subdivided by membranes into three fluid-filled chambers or canals (Figure 9.5b). In this illustration, the end of the cochlea has been removed, and you are looking down the three canals from the base end. The stirrup (see Figure 9.5a) rests on the *oval window*, a thin, flexible membrane on the face of the vestibular canal. The *vestibular canal* (scala vestibuli) is the point of entry of sound energy into the cochlea. The vestibular canal connects with the *tympanic canal* at the far end of the cochlea through an opening called the *helicotrema*. (You might not need to remember this term, but it just *sounds* too wonderful to leave out!) The helicotrema allows the pressure waves to travel through the cochlear fluid (called endolymph) into the tympanic canal more easily. Liquids are essentially incompressible; at the end of the tympanic canal, another thin membrane, the *round window*, flexes outward with each sound wave and allows the fluid to move. The vestibular organs on top of the cochlea do not participate in hearing; we will talk about them in Chapter 11.

All this activity in the vestibular and tympanic canals bathes the **cochlear canal**, where the auditory receptors are located, in vibration. The vibration passes to the **organ of Corti**, the sound-analyzing structure that rests on the **basilar membrane**. The organ of Corti consists of four rows of specialized cells called hair cells, their supporting cells, and the **tectorial membrane** above the hair cells (Figure 9.5c). To visualize these structures, remember that you are looking down a long tube; imagine the four rows of hair cells as upside-down combs and the tectorial membrane as a shelf stuck to the teeth.

? How is the auditory stimulus converted to a neural impulse?

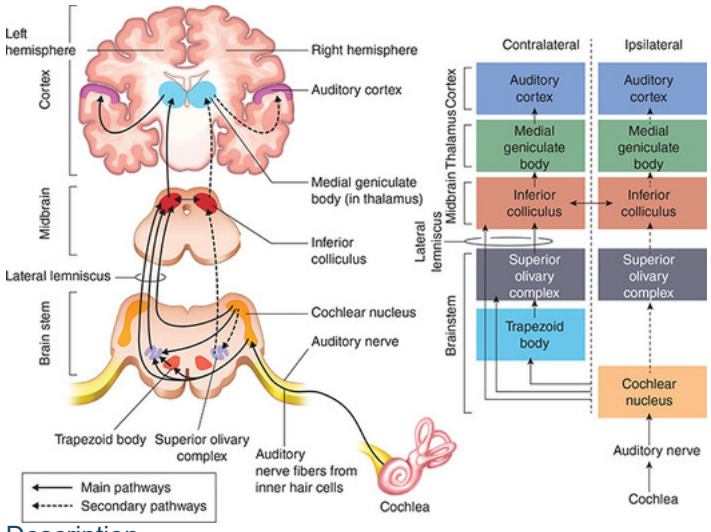
The hair cells are the mechanical receptors for auditory stimulation (Figure 9.5d). Vibration of the basilar membrane and the cochlear fluid bends the hair cells back and forth. Forward movement opens potassium and calcium channels (not sodium channels, as in neurons), and the inflow of ions depolarizes the hair cell membrane; backward movement closes the channels and hyperpolarizes the membrane (Müller, 2008). Depolarization results in neurotransmitter release and stimulation of the auditory neurons connected to the hair cells. The hair cells are very sensitive; the amount of movement required to produce a sensation is equivalent to the Eiffel Tower leaning just the width of your thumb (Hudspeth, 1989), about the distance the tower sways in a strong wind.

The human cochlea has two sets of hair cells: a single row of about 3,500 inner hair cells and three rows of about 12,000 outer hair cells (“inner” and “outer” refer to their location relative to the center of the coiled cochlea; see Figure 9.5c). The **inner hair cells** are the sensory cells; they receive 90% to 95% of the auditory neurons, and they provide most of the information about auditory stimulation (Purves et al., 2018). A strain of mouse lacking inner hair cells due to a mutant gene is unable to hear (Deol & Gluecksohn-Waelsch, 1979). When inner hair cells are destroyed by chronic exposure to loud sounds, disease, or certain drugs, they are not replaced. The **outer hair cells** increase the cochlea’s sensitivity, both by amplifying its output and by sharpening the frequency tuning at the location of peak vibration (Hudspeth, 2008; Z. Xiao & Suga, 2002). Experimentally induced damage to the outer hair cells causes a dramatic loss of hearing but also a loss of frequency selectivity along the basilar membrane. Why are these apparently non-sensory cells so important? Apparently,

the outer hair cells' tugging on the tectorial membrane increases stimulation of the inner hair cells located where the vibration is greatest.

Pathway to the Auditory Cortex and Beyond

The work of the auditory system is hardly finished when we have converted sound into electrical impulses. Neurons from the two cochleas make up part of the auditory nerves (eighth cranial nerves), one of which enters the brain on each side of the brain stem. The information from the cochleas passes through the lateral lemniscus to various brain stem nuclei (see Figure 9.6) to the inferior colliculi (which are involved in sound localization, as we will discuss later), then to the medial geniculate nucleus of the thalamus (where attentional processes interact with ascending auditory information), and finally to the auditory cortex in each temporal lobe. As you'll see in Chapters 10 and 11, the crossover of sensory information for opposite-side brain processing is a common occurrence. Therefore, a sound on your right side is registered primarily, but not exclusively, in the left hemisphere of the brain. Researchers interested in differences in function between the two hemispheres have used an interesting strategy, called the *dichotic listening task*, to stimulate one side of the brain. They present an auditory stimulus through headphones to one ear and present white noise (which contains all frequencies and sounds like radio static) to the other ear to occupy the nontargeted hemisphere. This technique has helped researchers determine that the left hemisphere is dominant for language in most people and that the right hemisphere is better at other tasks, such as identifying melodies. The auditory cortex is on the superior (upper) gyrus of the temporal lobe of each hemisphere; part of it is hidden inside the lateral fissure, as you can see in the figure.



Description

Figure 9.6 The Auditory Pathway and the Auditory Cortex.
Auditory information from the cochlea ascends through many brain areas before arriving at the auditory cortex. Most auditory information crosses to the opposite (contralateral) hemisphere between the cochlear nucleus and trapezoid body, but some stays on the same side (ipsilateral) as the cochlea.

The auditory cortex is **tonotopically organized**, which means that neurons from adjacent receptor locations project to adjacent cells, and they convey similar frequencies. In this case, the projections form a frequency map on the unrolled basilar membrane (Merzenich, Knight, & Roth, 1975), just as the somatosensory cortex contains a map of the body (see Chapter 3). When we study vision in Chapter 10, we will see that this map-like organization is typical in the senses.

Beyond the primary auditory cortex are additional processing areas, as many as nine in some mammals; these secondary auditory areas are involved in processing complex sounds and understanding their meaning. For example, some of the cells adjacent to the monkey's primary auditory area respond selectively to calls of their own species, and some of those react only to one type of call (Wollberg & Newman, 1972). Similarly, songbirds are sensitive to their own personal songs in the midbrain auditory areas (Poirer, Boumans, Verhoye, Balthazart, & Van der Linden, 2009). The human primary auditory cortex has a secondary area surrounding it (Figure 9.6), but auditory information also travels well beyond the auditory areas, following the *dorsal stream* or the *ventral stream* (Alain, Arnott, Hevenor, Graham, & Grady, 2001; Rauschecker & Tian, 2000).

The dorsal stream flows from the auditory cortex through the parietal area, where the brain combines information from other senses to locate the sound in relation to the body and the visual scene. The information then proceeds to the frontal lobes, where it can be used for directing eye movements toward sound sources and for planning movements. The ventral stream is active when the individual is identifying sounds; the call-specific cells of the monkey's auditory system are part of this system. Because of their specialties, the ventral and dorsal streams have been dubbed the "what" and "where" systems of audition, identifying what the sound is and where its source is located. These two pathways are illustrated in Figure 9.7. We will consider the communication roles of the dorsal and ventral streams later, in the section on language, and you will see in Chapter 10 that vision has similar systems.

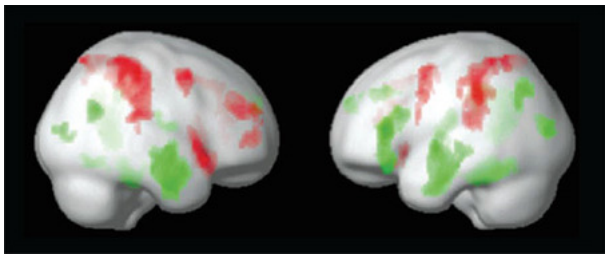


Figure 9.7 The Dorsal "Where" and Ventral "What" Streams of Auditory Processing. The red areas were active when subjects determined the locations of sounds. Green areas were activated when they identified sounds. Localization and identification followed dorsal "where" and ventral "what" streams, respectively, with both terminating in frontal areas. (Functional MRI data were superimposed over a smoothed image of a brain.)

Source: From "Distinct Pathways Involved in Sound Recognition and Localization: A Human fMRI Study," by P. P. Maeder, R. A. Meuli, M. Adriani, A. Bellmann, E. Fornari, J.-P. Thiran, A. Pittet, and S. Clarke, 2001, *NeuroImage, 14*, pp. 802–816. Used with permission from Elsevier.

Frequency Analysis

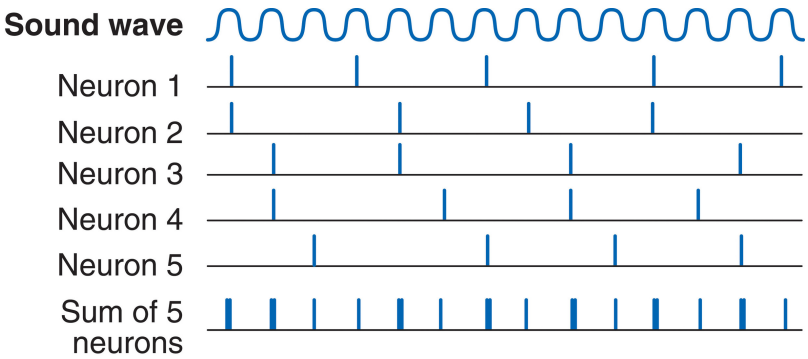
Now that we have gone over the anatomy of the auditory system and processing areas in the brain, we can examine some of the functional aspects of the auditory system. Before we get to the more complex concepts on how our brains extract information from the cochlea to determine the location and meaning of sound, we first must discuss how the vibrations of the conducting medium are converted into neural impulses by the cochlea. To do this, the cochlea is built to extract both frequency and intensity information from the sound through the movement of hair cells spread out across the length of the cochlea. More than 50 years ago, Ernest Wever (1949) described 17 versions of the two major theories of frequency analysis, which indicates the difficulty we have had in figuring out how people experience pitch. We will discuss a few versions that have been important historically. Besides introducing you to these two important theories, we will describe what we know about how the auditory mechanism works and give you some idea of how theories develop in response to emerging evidence.

Telephone and Frequency Theories

The most obvious explanation of how the auditory system analyzes frequency is the **frequency theory**, which assumes that the auditory mechanism transmits the actual frequency of a sound to the auditory cortex for analysis there. William Rutherford proposed an early version in 1886; it was called the **telephone theory** because he believed that individual neurons in the auditory nerve fired at the same frequency as the rate of vibration of the sound source. Half a century later, it was possible to test the theory with electrical recording equipment. Ernest Wever and Charles Bray (1930) performed one of the most intriguing investigations of auditory frequency analysis found in the scientific literature. They attached an electrode to the auditory nerve of an anesthetized cat and recorded from the nerve while they stimulated the cat's ear with various sounds. Because the simple equipment used to record neural activity at that time was limited to very low frequencies, Wever and Bray ran the amplified neural responses into a telephone receiver in a soundproof room and listened to the output. Sounds produced by a whistle were transmitted with great fidelity. When someone spoke into the cat's ear, the speech was intelligible, and the researchers could even identify who the speaker was. They concluded the auditory nerve was "following," or firing at the same rate as, the auditory stimulus frequencies. It appeared that the telephone theory was correct, but with the benefit of our more modern understanding of neural functioning, we all now know that single neurons cannot possibly fire at such high rates. (See the discussion of refractory periods in Chapter 2 if you don't remember.)

? How do the frequency and place theories explain frequency analysis?

Obviously, Wever and Bray were recording not from a single neuron but from all the neurons in contact with the hook-shaped copper electrode they placed in contact with the auditory nerve. Thus, they were monitoring the *combined* activity of hundreds, perhaps thousands of neurons. Wever explained their finding later in his **volley theory**, which states that groups of neurons follow the frequency of a sound at higher frequencies when a single neuron cannot (Wever, 1949). A group of neurons can follow high frequencies because different neurons "take turns" firing. The term *volleying* is analogous to playing volleyball, where players take turns when striking the ball to keep it aloft. Volleying is illustrated in Figure 9.8, where each of the neurons synchronizes its firing to the wave peaks of the tone; no single neuron can fire on every peak, but at least one neuron will be firing on each wave peak. In this theory, the brain then combines information from many neurons to determine the tone's frequency. In Wever and Bray's study, volleying in the auditory nerve was unable to keep up with the sound frequency beyond 5200 Hz, a figure that subsequent research has shown to be quite accurate (J. E. Rose, Brugge, Anderson, & Hind, 1967). So even with volleying, frequency following can account for only one fourth of the range of frequencies we hear.



Description

Figure 9.8 Illustration of Volleying in Neurons.
No single neuron can respond to each peak of a high-frequency sound, but a group of neurons can. The representative neurons 1–5 would be in the cochlea, whereas the summation neuron might be in the auditory midbrain.

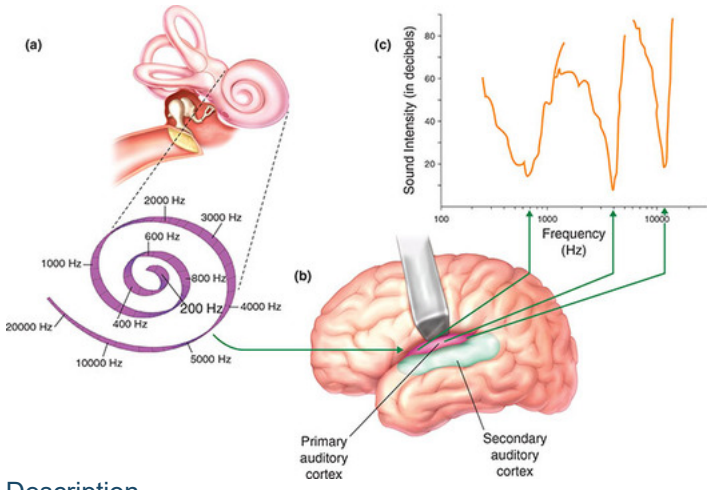
Place Theory

In the 19th century, Hermann von Helmholtz (1863/1948) proposed that the basilar membrane was like a series of piano strings, stretched progressively more loosely with distance down the membrane. Then he invoked a principle from physics called *resonance* to explain how we discriminate different frequencies. Resonance is the vibration of an object in sympathy with another vibrating object. If you pluck the strings of a guitar, you will notice that the strings begin to vibrate. The thinner, more tautly stretched E string vibrates faster and has a higher pitch and frequency than the thicker, less tautly stretched G string. According to Helmholtz, resonance would cause the narrow base end of the membrane to resonate more to high-frequency sounds, the middle portion to moderate frequencies, and the wider apex (tip) to the lowest frequencies. Helmholtz's proposal was a type of **place theory**, which states that encoding sound frequency depends on the location of maximal vibration on the basilar membrane; the more a particular section of membrane vibrates, the higher the levels of firing in the hair cells found there. Place theory in its evolving versions has been the most influential explanation of frequency analysis for a century and a half. It is another example of a scientific idea that has become almost universally accepted but continues to be referred to as a theory.

A century later, Georg von Békésy (a communications engineer from Budapest) began a series of innovative experiments that won him the Nobel Prize for physiology in 1961. Békésy constructed mechanical models of the cochlea and observed the responses of the basilar membrane in cochleas he removed from deceased subjects as diverse as elephants and humans. When he stimulated these cochleas with a vibrating piston, he could see under the microscope that vibrations peaked at different locations along the basilar membrane; a wavelike peak hovered near the base when the frequency was high and moved toward the apex when Békésy (1951) decreased the frequency. But Helmholtz was wrong about the basilar membrane being like a series of piano strings; Békésy (1956) determined that its frequency selectivity is due to differences in elasticity, with the membrane near the stirrup 100 times stiffer than at the apical end.

Figure 9.9a shows how frequency sensitivity is distributed along the membrane's length (see Figure 9.5 again for the location of the basilar membrane). Recordings from single auditory neurons have confirmed that place information about frequency is preserved in all lower levels of auditory processing, from the cochlea to the auditory cortex. In other words, these structures contain a *tonotopic map*, which means that each successive area responds to successively higher frequencies (Figure 9.9a and 9.9b).

Figures Brought to Life



Description

Figure 9.9 Frequency Sensitivity of the Basilar Membrane and Auditory Cortex. In (a), notice that the basilar membrane is narrower at the base end of the cochlea and widens toward the apex, the opposite of the cochlea's shape. Its frequency selectivity is preserved in the tonotopic map seen in the auditory cortex. In (b), the part of the auditory cortex at the left end of this view receives neurons from the apex of the cochlea, and the other end responds to signals from the base. The auditory cortex thus forms a "map" of the basilar membrane so that each successive area responds to progressively higher frequencies. In (c), we show the frequency sensitivities of three representative neurons in the auditory cortex. The lowest point of each curve indicates that neuron's primary frequency and the lowest amplitude of sound that will activate the neuron. Other frequencies within the curve will also activate that neuron, but activation decreases with distance from the primary frequency.

You can see from the *tuning curves* in Figure 9.9c that each neuron responds most to a narrow range of frequencies (Palmer, 1987), due to the neuron's place of origin in the cochlea. However, each neuron also responds to a lesser extent to a range of frequencies around its "primary" frequency, mirroring the pattern of vibration in the basilar membrane. So how can neurons that make such imperfect discriminations inform the brain about the frequency of a sound with the 2- to 3-Hz sensitivity that has been observed? The answer is lateral inhibition; the more highly stimulated neurons inhibit activity in adjacent neurons with slightly different primary frequencies (G. Wu, Arbuckle, Liu, Tao, & Zhang, 2008). As a result, some neurons in the auditory cortex are many times more discriminating than neurons in the auditory nerve (E. L. Bartlett, Sadagopan, & Wang, 2011; Bitterman, Mukamel, Malach, Fried, & Nelken, 2008). This neural sharpening of information is a characteristic of most sensory systems, as we will see when we discuss sound localization and in Chapter 10 when we talk about vision.

Place analysis is the reason we can hear with some clarity through bone conduction. The vibrations enter the cochlea from all sides during bone conduction, rather than through the oval window, but Békésy (1951) demonstrated with his cochleas that the tonotopic response of the basilar membrane is independent of sound source. As he moved his vibrating piston from the base around to the side of the cochlea, or to the apex or anywhere else, the peak of vibration remained in the same location. Thomas Edison was nearly deaf, yet his second most famous invention was the phonograph. He compensated for his impaired hearing by grasping the edge of the phonograph's wooden case between his teeth and listening to the recording through bone conduction. You can still see the bite marks on one of his phonographs in the museum at his winter home and laboratory in Fort Myers, Florida. Figure 9.10 shows a device that takes advantage of bone conduction; new hearing aids such as the Osia 2 use bone conduction to restore hearing (Cochlear Limited, 2019).

Figure 9.10 A Bluetooth Headset That Works by Bone Conduction.
Like other Bluetooth headsets, the Trekz Titanium headset can connect to all your auditory devices. However, rather than using speakers, this device transmits sound directly to the cochlea through the skull, which means that your ears are unobstructed.

Source: Hugh Threlfall/Alamy Stock Photo.

Combining Theories

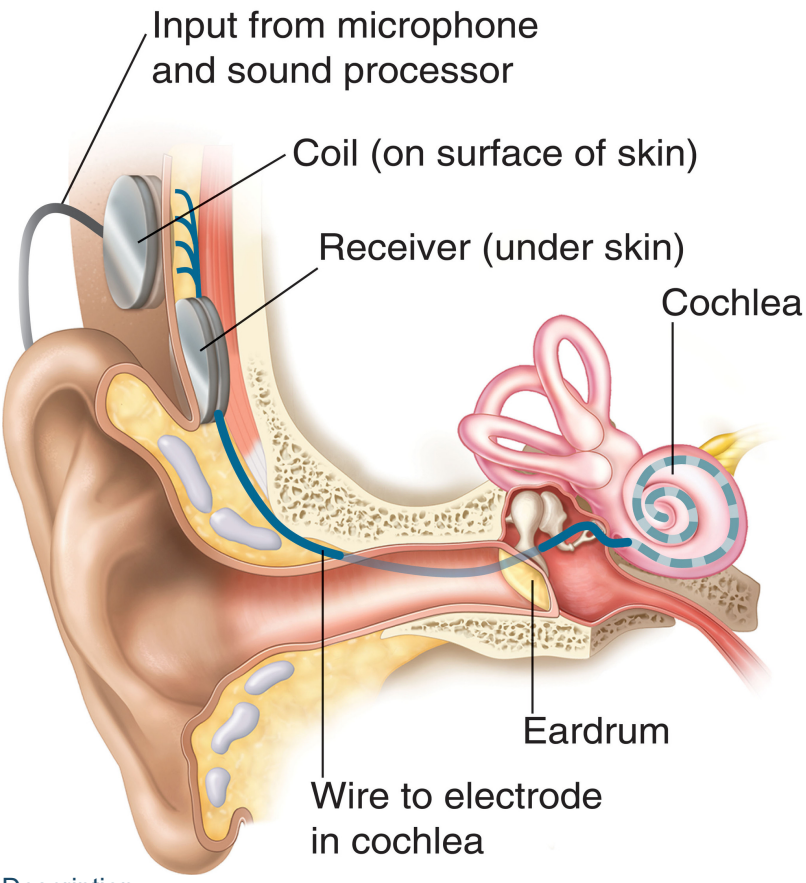
At low frequencies, the entire basilar membrane vibrates about equally, and researchers have been unable to find neurons that are specific for frequencies below 200 Hz (Kiang, 1965). Wever (1949) suggested a *frequency-volley-place theory*: Individual neurons follow the frequency of sounds up to about 500 Hz by firing at the same rate as the sound's frequency; then between 500 and 5000 Hz, the frequency is tracked by volleying (combining the responses from multiple neurons), and place analysis takes over beyond that point. While volleying does occur in the auditory nerve, studies do not show that the brain uses that information in frequency analysis. Therefore, most researchers subscribe to a simpler **frequency-place theory** : Frequency following by individual neurons accounts for frequencies up to about 200 Hz, and all remaining frequencies are represented by the place of greatest activity.

Fortunately, we can sum up the auditory system's handling of intensity coding much more simply. As we learned in Chapter 2, a more intense stimulus causes a neuron to fire at a higher rate. The auditory system relies on this strategy for distinguishing among different intensities of sound. However, this is not possible at lower frequencies, where firing rate is the means of coding frequency. Researchers believe that at the lower frequencies, the brain relies on the number of neurons firing as increases in stimulus intensity recruit progressively higher-threshold neurons into activity.

Restoring Hearing

For individuals who have damage to the middle ear bones or a mild loss of hair cells due to aging, a simple hearing aid does an excellent job in compensating for the loss of amplification. However, 90% of hearing impairment cases involve loss of hair cells, and because hair cells don't regenerate, these individuals may be candidates for a cochlear implant, like Millicent Simmonds's and the ones worn by the two children in the opening photograph for this chapter. An implant uses a microphone to pick up sounds and send them to a speech processor located behind the ear; then a

transmitter on the surface of the skin sends the signal to a receiver that is surgically embedded under the skin (Figure 9.11). From there, the signal travels to an electrode array threaded through the cochlea; these electrodes deliver signals representing the different sound frequencies to different basilar membrane locations. Activating different neurons with different frequencies mimics the functioning of the basilar membrane and hair cells in an unimpaired individual; in other words, it relies on the principle of place analysis.



Description

Figure 9.11 A Cochlear Implant.

A microphone and speech processor on the surface send the information to a receiver implanted under the skin. Wires from the receiver distribute electrical signals along the basilar membrane according to their frequencies.

Most cochlear implant recipients hear effectively enough to use a telephone, which is more difficult than face-to-face conversation; most children can be mainstreamed in school, and they rate their quality of life comparably with their peers (Loy, Warner-Czyz, Tong, Tobey, & Roland, 2010). Early implantation works best, because hearing and language development both depend on early auditory feedback and because neurons from other sensory areas can reorganize the unused auditory cortex over time (D. S. Lee et al., 2001). In adults, success also depends on having learned language before deafness occurred. Children, by contrast, can use the implants regardless of whether they learned language previously (Francis, Koch, Wyatt, & Niparko, 1999).

Conventional implants have a number of disadvantages: they are bulky and cumbersome, only a few can be worn in the shower or while swimming, and the wearer is likely to experience some amount of social stigma. Researchers at Harvard University and the Massachusetts Institute of Technology are developing a fully

implantable device (Yip, Jin, Nakajima, Stankovic, & Chandrakasan, 2015), though a commercially available device is still years away. A tiny sensor mounted on the malleus detects the movement of the ossicles, and a processor-on-a-chip turns the vibrations into signals that are delivered to the cochlear nerve. The device consumes very little power, and it is anticipated that it would be charged overnight by sleeping on a special pillow. But there are additional problems with the quality of reproduction; A Further Look describes some of the ongoing efforts to improve cochlear implants and eventually make them obsolete.

A Further Look:

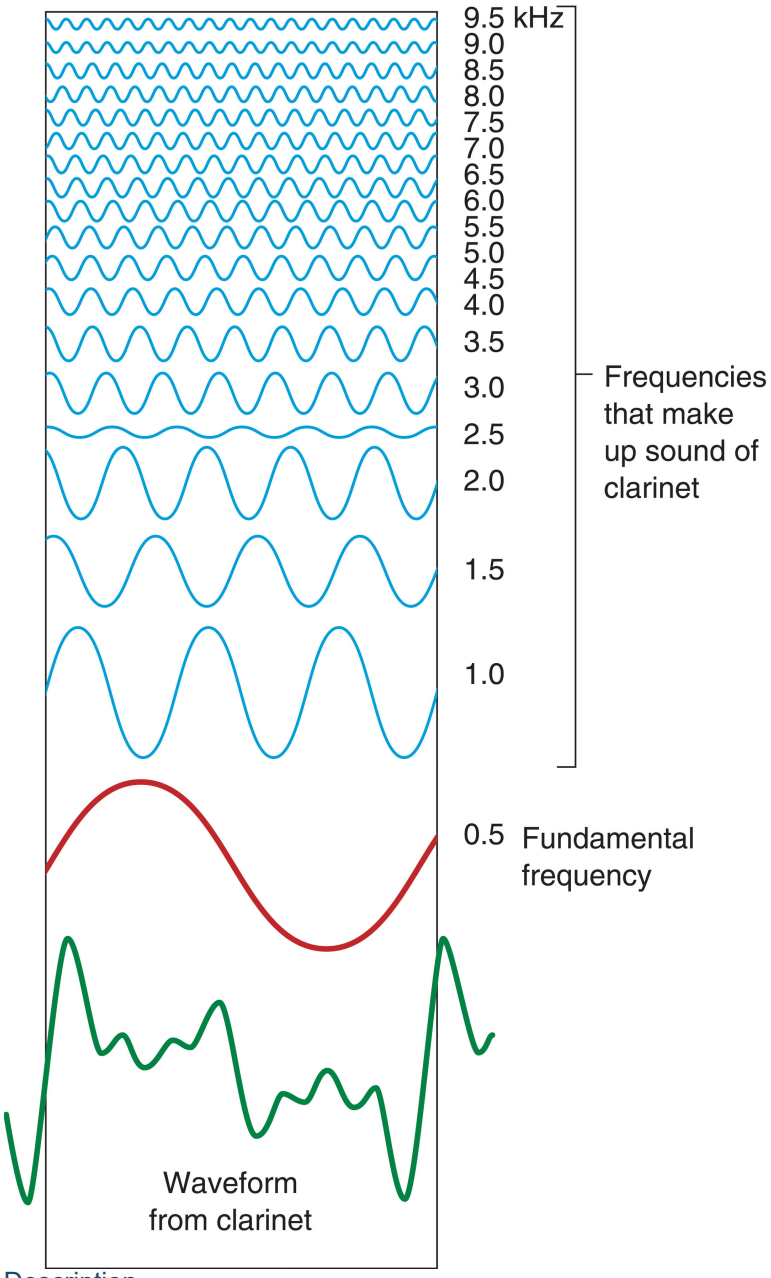
Beyond Cochlear Implants

A major problem people have with cochlear implants is difficulty following conversations in a crowded or noisy environment. A recent study with marmosets suggests that although implants restore some hearing, they activate too few auditory neurons to provide adequately clear audition (L. A. Johnson, Della Santina, & Wang, 2016). Imagine, for example, what your photos would look like if your smartphone was limited to displaying them in a few hundred pixels instead of the usual few million. You would see the outlines of objects and some of the features, but most of the detail would be gone. Because hearing is less than optimal with current cochlear implants, researchers continue to improve them. One potential improvement involves adding neurotrophins (see Chapter 3) to the cochlear implant itself to help regenerate and repair weak neurons (Pinyon et al., 2014).

In the future, gene replacement may be an additional option. Inserting genes to replace damaged hair cells improved hearing in mice to a point equivalent to the ability to hear a loud conversation (György et al., 2017). Based on successes like this, Columbia University has begun the world's first gene therapy trial for hearing loss in humans (Columbia University, n.d.). Gene therapy carries some risks that could prevent its use in humans; one alternative is stem cell therapy. In animal studies, stem cells have developed into hair cells and auditory neurons and have improved lost hearing (Dufner-Almeida et al., 2019). In the first published human trial, children received stem-cell-rich umbilical cord blood; they experienced neural improvements, such as shorter cochlear nerve latencies, which could have been due to increased hair cells (L. S. Baumgartner et al., 2018). Safer still might be inducing hair cells to develop from existing progenitor cells, cells that are intermediate between stem cells and hair cells. Treating mouse cochlear tissue with the chemical y-secretase caused some of the basilar membrane cells to develop into hair cells (Mizutari et al., 2013). A Phase 1 trial using the compound FX-322 with humans resulted in improved sound clarity and word understanding, and a Phase 2 trial is expected to be completed by Fall 2020 (Frequency Therapeutics, 2019).

Analyzing Complex Sounds

You may have realized that we rarely hear a pure tone. The speech, music, and noises that are so meaningful in our everyday lives are complex, made up of many frequencies. Yet we have an auditory mechanism that appears to be specialized for responding to individual frequencies. A solution to this enigma was suggested even before Helmholtz proposed his place theory. The French mathematician Joseph Fourier had demonstrated 40 years earlier that any complex waveform—sound, electrical, or whatever—is in effect composed of two or more component sine waves. *Fourier analysis* is the analysis of a complex waveform into its sine wave components (Figure 9.12). Georg Ohm, better known for Ohm's law of electricity, proposed a few years later that the ear performs a Fourier analysis of a complex sound and sends information about each of the component frequencies to the cortex. Current researchers agree that the basilar membrane acts as the auditory Fourier analyzer, responding simultaneously along its length to the sound's component frequencies.



Description

Figure 9.12 Fourier Analysis of a Clarinet Note.
The dominant component is a relatively high-amplitude, low-frequency sine wave; the other components are progressively higher frequencies at lower intensities. If we produced sounds at each of these frequencies and amplitudes at the same time, the combined waveform when displayed on an oscilloscope would look like the waveform at the top, and the result would sound like the clarinet note.

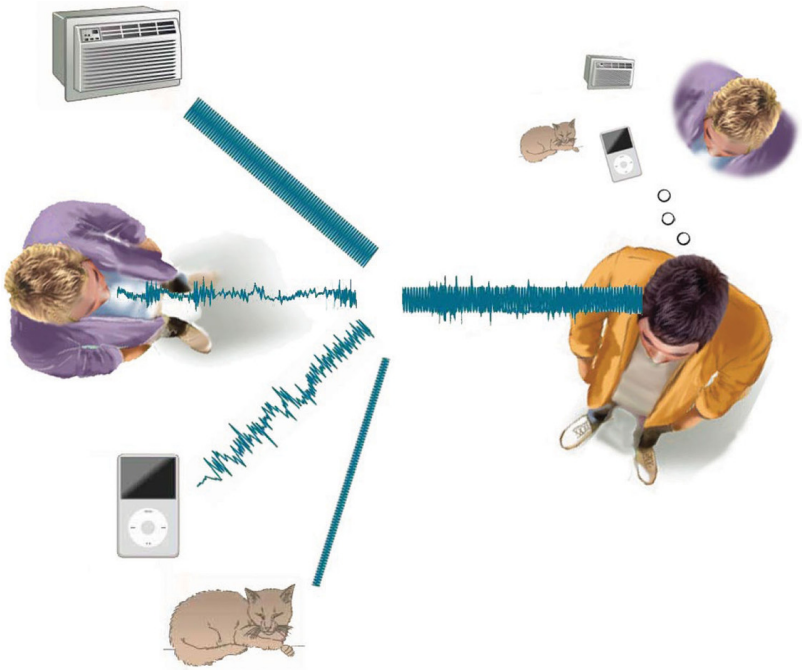
Source: From "How Much Distraction Can You Hear?" by P. Milner, *Stereo Review*, June 1977, pp. 64–68. © 1977.

? How does the auditory system handle complex sounds?

Not only do we rarely hear a pure sound; we also seldom hear a single complex sound by itself. All the sounds in our environment at one time make up the *auditory*

scene. At a party, we simultaneously hear the music playing loudly, multiple conversations going on all around us, as well as general sounds of people moving about, dancing, eating, and drinking. Despite the number of complex sounds assaulting our cochleas, we can separate our conversations with fellow partygoers from the other noises in the room. And we do more than that; we periodically sample the other sounds regularly enough to enjoy the music and to hear snippets of conversation near us. The ability to sort out and focus on meaningful auditory messages from a complex background of sounds is referred to as the **cocktail party effect**. This ability isn't unique to humans; dogs use it to hear their names over background noise in a crowded room, and it enables frogs to find mates among a chorus of frogs (Farris and Ryan, 2011; Mallikarjun, Shroads, & Newman, 2019; R. C. Taylor, 2017).

Think of all the sound sources around you as an *auditory scene*, comparable to a visual scene. In Figure 9.13, all the sound sources surrounding Sam make up his auditory scene. Each makes its own characteristic sound, but at his ear, these are all blended into seemingly indistinguishable noise. But Sam can deconstruct this noise into its original components. He can also carry on a conversation with Roger, ignore the noisy air conditioner, and still recognize his favorite song when it comes up in his playlist or notice that the cat is purring softly in the corner. Here it is useful to think in terms of an **auditory object** —a sound we identify as distinct from other sounds. This is no simple process; it requires identifying characteristics such as pitch, rhythm, and tempo, aided by our ability to separate sounds by their directional location.



Description

Figure 9.13 Analysis of a Complex Auditory Scene.
All the sounds in the auditory scene blend into a very complex waveform, but Sam is able to separate them and identify the individual auditory objects. This also allows him to attend to what his friend Roger is saying, to the virtual exclusion of the other sounds.

So how does the brain do this? Sounds are distinguished from each other by their frequency, intensity, timbre, location, and novelty; all these are processed in the auditory cortex and in the broader ventral "what" pathway (see Figure 9.14; Christison-Lagay, Gifford, & Cohen, 2015). Once an object has been selected for attention—based on the hearer's motivation, or perhaps because the sound is novel or loud—its neural signals are enhanced and those of other objects suppressed at multiple levels of the auditory system. This begins among the outer hair cells, which

we learned earlier modulate the frequency responsiveness of the basilar membrane. The auditory cortex sends signals back to the outer hair cells, and their action enhances frequency sensitivity in specific areas (Z. Xiao & Suga, 2002). When patients fitted with cortical electrodes to locate the source of their seizures attended to one of two speech sources, that speech was tracked closely in the auditory cortex, while the competing speech was somewhat suppressed at lower levels of the auditory system. In higher-order areas, including those concerned with language, the unattended speech dropped out completely (Horton, D'Zmura, & Srinivasan, 2013; Zion Golumbic et al., 2013).

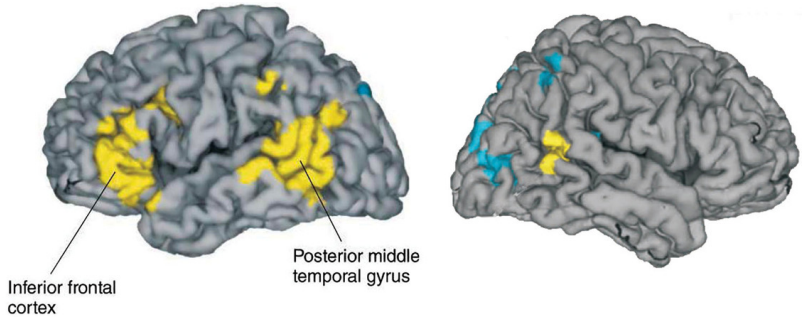


Figure 9.14 Areas Involved in Identifying Environmental Sounds.
Recognized sounds activated the areas in yellow; unrecognized sounds activated the other areas (blue), mostly in the right hemisphere. Notice that the activity occurs mostly in the ventral "what" pathway.

Source: From "Human Brain Regions Involved in Recognizing Environmental Sounds," by J. W. Lewis et al., 2004, *Cerebral Cortex, 14,* pp. 1008–1021, by permission of Oxford University Press.

? How does the brain determine the locations of sounds?

Locating Sounds

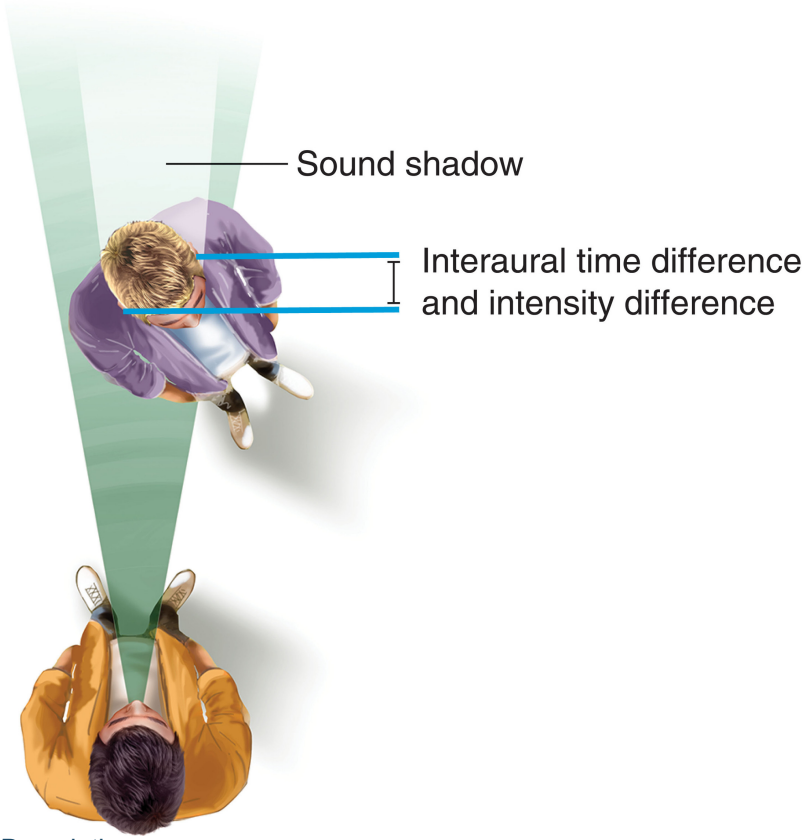
The most obvious way to locate a sound is to turn your head until the sound is loudest. This is not very effective, because the sound may be gone (or the car may have hit you) before the direction is located. Three additional cues permit us to locate sounds quickly and accurately (Risoud et al., 2018). Two of these rely on the fact that our hearing is binaural, meaning that we have two ears; the brain determines the location based on acoustic differences between the two ears. Animals with ears that are very close together (such as mice) are at a disadvantage in locating sounds because the differences are so small. Grasshoppers and crickets have evolved a compensation for their small head size: Their auditory organs are on their legs, as far apart as possible. Nineteenth-century sailors used a novel application of this strategy when they needed to locate the direction a distant ship or foghorn: They listened through tubes attached to funnels at the ends of a long rod called a topophone (Figure 9.15).

Description

Figure 9.15 Sound-Localizing Device Used by 19th-Century Sailors.
By listening through devices on a long rod (called a topophone), sailors effectively increased the distance between their ears and enhanced the binaural cues.

Source: From "Navigation in Fog," *Scientific American*, July 3, 1880, p. 3.

When a sound source is on one side, the head blocks some of the sound energy. The sound shadow this creates produces an **interaural level difference**, so that the near ear receives a more intense sound (Figure 9.16). Some of the neurons in the superior olivary nucleus, located in the brain stem, respond to differences in intensity at the two ears; this works by a simple subtraction mechanism, with excitation from the far ear being excitatory and from the near ear being inhibitory (Grothe & Pecka, 2014). Because low-frequency sounds tend to pass through solid objects such as the head with little attenuation, intensity difference serves as a reliable cue only above 2000 Hz.



Description

Figure 9.16 Differential Level and Timing as Cues for Sound Localization.
The sound is reduced in intensity and arrives later at the distant ear.

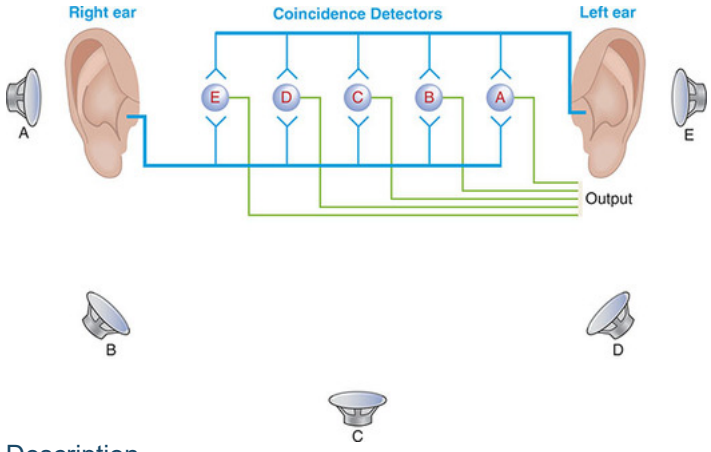
The second binaural cue for locating sounds is **interaural timing difference (ITD)** at the two ears. A sound that is directly to a person's left or right takes about 0.5 milliseconds to travel the additional distance to the second ear (see Figure 9.16 again); humans can detect an interaural timing difference as small as 10 microseconds (millionths of a second; Hudspeth, 2013), which means we can locate sound sources that move by as little as a degree horizontally. This computation also is done in the superior olivary nucleus (Grothe & Pecka, 2014; Masterton, Jane, & Diamond, 1966). Time differences are most useful below about 1500 Hz (Risoud et al., 2018).

These two cues are extremely good at distinguishing left from right, but they cannot tell you whether a sound is in front of, behind, above, or below you. **Head-related transfer function (HRTF)** refers to frequency alterations to a sound as it passes through the pinna and auditory canal, as well as through the head and other parts of the body. Some frequencies in a complex sound will be attenuated and others amplified, and the pattern will depend on the angle of passage and the body parts involved. Combining HRTF with level and time differences provides the brain with a three-dimensional map of the auditory space. Some home audio systems use HRTF to reproduce surround sound from headphones.

A Brain Circuit for Detecting Time Differences

The intensity and time differences we're talking about are extremely subtle; they are well below our ability to process consciously and require detection by specialized circuits. The circuit for interaural timing difference has been studied the most

thoroughly and has been mapped in the barn owl, which can locate a mouse in darkness just from the sounds it makes rustling through the grass. The circuit is in the nucleus laminaris, the avian (bird) counterpart of the mammalian superior olivary nucleus. Electrical recording has revealed the functioning of its **coincidence detectors**, neurons that fire most when they receive input from both ears at the same time (C. E. Carr & Konishi, 1990). Figure 9.17 is a simplified diagram of the circuit. When the sound comes directly from the left side of the figure (Speaker A), Detector A will receive stimulation simultaneously from the two ears, and the simultaneous inputs will cause the neuron to fire at a high rate. The stimulation is simultaneous because the connection between the near ear and the coincidence detector acts as a delay line, compensating for the delay in the sound reaching the distant ear. Likewise, Detector B will fire at its highest rate when the sound comes from Speaker B. When the sound source is equidistant from the two ears (such as directly in front of or behind the head), Detector C is most active, and so on. This circuit is another example of the neural enhancement of small sensory differences that we referred to earlier.



Description

Figure 9.17 A Circuit for Detecting Interaural Timing Differences.
The circuit's arrangement compensates for the greater travel time to the more distant ear. Try tracing the flow of activity through this diagrammatic representation of the circuit to determine which detector will fire most when sound comes from each of the speakers. (The speakers are at the same horizontal level as the ears.)

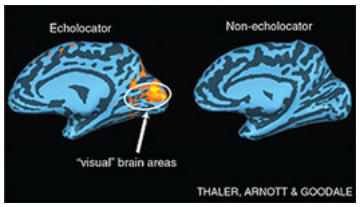
Source: Based on the results of C. E. Carr and Konishi (1990).

A full understanding of one's auditory scene requires integrating the direction of auditory objects with information from the visual environment and information about the position of the body in space. In Chapter 3, you learned that combining all this information is the function of association areas in the parietal lobes. So unlike identifying sounds, locating sounds in space occurs in the dorsal "where" stream.

The ultimate in sound localization is *echolocation*, a sort of sonar that bats, dolphins, whales, and some cave-dwelling birds use to avoid obstacles and to detect prey and predators. Bats are so proficient that they can use the echoes of their ultrasonic chirps to catch insects while avoiding obstacles such as tree limbs and telephone wires in total darkness (see Ulanovsky & Moss, 2008, for more information about these amazing mammals). Echolocation isn't unique to nonhumans; as you'll see in A Further Look, some blind individuals use it to avoid obstacles, and manufacturers are designing devices to make that easier.

A Further Look:

I Hear a Tree Over There



Some blind individuals have a remarkable ability to avoid obstacles in their paths, often without any awareness of how they do so. In 1749, the French philosopher Denis Diderot (1749/1916) studied one of these adept individuals and concluded that he relied on air currents deflected by the obstacles. By the time Karl Dallenbach and his colleagues tackled the question at Cornell University, 14 theories had been proposed (Supa, Cotzin, & Dallenbach, 1944) to explain how blind subjects could detect a wall from several feet away. They demonstrated that the subjects accomplished this by listening to the sounds of their footsteps reflected by the obstacle as they approached. Their performance was surprisingly good even when they listened from another room through headphones as an experimenter carrying a microphone walked toward the wall.

Blind individuals may use echolocation passively—simply listening for reflected sounds in their environment—or actively, by tapping a cane or scuffing their feet on the pavement, but these efforts can be thwarted by thick carpeting or a blanket of snow. Researchers have found that humans echolocate better by vocalizing instead of passively listening (Flanagin et al., 2017), and Daniel Kish is a living example of this principle. Daniel lost his eyes to cancer at the age of 1, but he grew up surprisingly normally, even riding a bicycle to school (D. Kish, 2013). It wasn't until he was 11 that a friend pointed out to him that he was using echolocation, clicking his tongue two to three times per second and listening for the echoes. As an adult, he bikes in busy traffic, travels by plane without assistance, and hikes in the woods, where he can recognize trees by the difference in the way the leaves and the trunks reflect the sounds. An fMRI study showed that blind individuals like Kish engage part of the visual cortex during echolocation, an area that is well suited for processing spatial information (see figure; Thaler, Arnott, & Goodale, 2011).

There are electronic devices on the market that emit ultrasonic signals and alert the wearer with an increasing tone or vibration rate as an object gets closer, but they don't provide a three-dimensional view of the environment. Kish has worked with two other blind echolocators and researchers to measure the frequencies (2–4 KHz and 10 KHz) and duration (~3 msec) of their clicks to help design better electronic devices (Thaler et al., 2017).

If this were the end of our discussion of audition, it would also be the end of the chapter, and, obviously, it is not. In humans, the most elaborate processing of auditory information occurs in language, which is our next topic.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

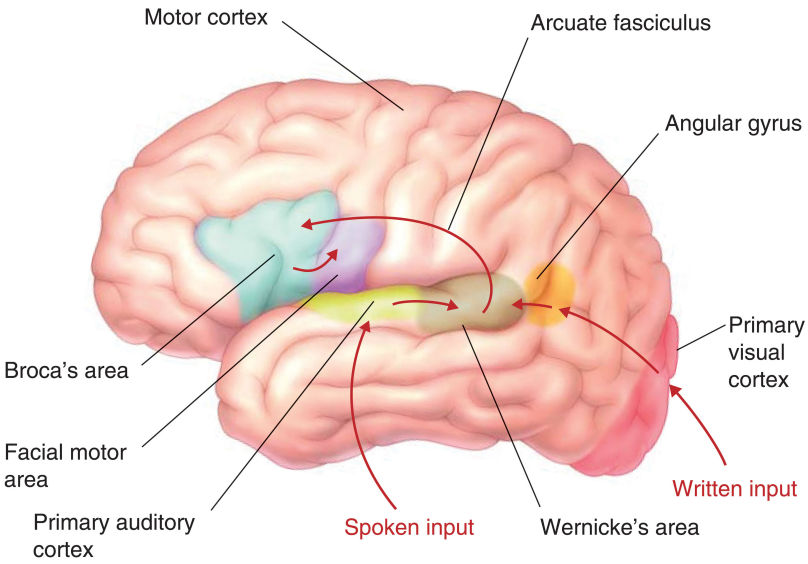
- Trace an auditory stimulus from the pinna to the auditory neurons in the cortex.
- Explain how, according to place theory, the frequency of sound is coded. How does the cochlea handle complex sounds?
- Explain how the circuit for detecting interaural timing difference works.

LANGUAGE

Now that we have gone over the fundamentals of the auditory system, let's apply this knowledge to a related topic, language. Keep in mind the meaning of the term **language** : a structured system of communication with a common set of grammatical, lexical, and organizational rules. It is not limited to speech but includes the generation and understanding of written, spoken, and gestural forms of communication. Language has important survival value and is inestimably important to human social relationships. A person who cannot communicate his or her thoughts to others suffers a high degree of isolation; one who cannot comprehend the communications of others is worse off still. These capabilities not only require learning; they also depend on specific structures of the brain, and damage to these structures can deprive a person of some or all of these functions.

Every language is characterized by a consistent set of rules, called **grammar**. This grammar can be quite flexible yet still convey the ideas and meaning of the speaker, which is called semantics. For instance, the *Star Wars* character Yoda frequently speaks with altered grammar in sentences like "See you I do," but the semantic meaning is clear. The individual sound units that comprise a language are called phonemes. Phonemes are small units of speech sound that distinguish one word from another—for example, the beginning sounds that distinguish *book*, *took*, and *cook*. Phonemes can be combinations of consonants and vowels (and even clicks!) and vary in languages from less than 20 in Polynesian languages (such as Hawai'ian) to more than 80 in Taa (spoken in Botswana and Namibia).

In 1861, the French physician Paul Broca reported his observations of a patient who for 21 years had been almost unable to speak. Tan, as the hospital staff knew him because that was one of the few sounds he could make, died shortly after he came under Broca's care. The autopsy revealed that Tan's brain damage was in the posterior portion of the left frontal lobe. After studying eight other patients, Broca concluded that **aphasia** —language impairment caused by damage to the brain—results from damage to the frontal area anterior to the motor cortex, now known as *Broca's area*. Nine years later, a German doctor named Carl Wernicke identified a second site where damage produced a different form of aphasia. Located in the posterior portion of the left temporal lobe, this site is known as Wernicke's area. See Figure 9.18 to locate Broca's and Wernicke's areas and the other structures to be discussed here. Most of our understanding of the brain structures involved in language comes from studies of brain-damaged individuals, so this is where we will start.



Description

Figure 9.18 Language-Related Areas and the Wernicke-Geschwind Model. Verbal input arrives in the auditory cortex and then travels to Wernicke's area for interpretation. Written input arrives there via the visual cortex and angular gyrus. If a

verbal response is required, Wernicke's area sends output to Broca's area for articulation of the response, and the facial area of the motor cortex produces the speech.

Source: Adapted from "Specializations of the Human Brain,' by N. Geschwind, *Scientific American*, 241 (9), pp. 180-199.

Carolina Hrejsa/Body Scientific Intl.

Broca's Area

Broca's aphasia is language impairment caused by damage to Broca's area and surrounding cortical and subcortical areas. The symptoms can best be understood by examining the speech of a stroke patient; as you read this interview, you will see why the disorder is also referred to as *expressive aphasia*.

? What are the differences between Broca's aphasia and Wernicke's aphasia?

Doctor: What happened to make you lose your speech?

Mr. Ford: Head, fall, Jesus Christ, me no good, str, str … oh Jesus … stroke.

Doctor: I see. Could you tell me, Mr. Ford, what you've been doing in the hospital?

Mr. Ford: Yes, sure. Me go, er, uh, P.T. nine o'cot, speech … two times … read … wr … ripe, er rike, er, write … practice … getting better. (H. Gardner, 1975, p. 61)

Mr. Ford's speech was not nearly as impaired as Tan's; he can talk, and you can get a pretty good idea of his meaning, but he showed the classic symptoms associated with damage to Broca's area. First, his speech was *non-fluent*. Although well-practiced phrases such as "yes, sure" and "oh, Jesus" come out easily, his speech was halting, with many pauses between words. Second, he had trouble finding the right words, a symptom known as *anomia* ("without name"). He had *difficulty with articulation*; he mispronounced words, such as "rike" for *write*. Finally, notice that his speech was *agrammatic*; it had content words (nouns and verbs) but lacked grammatical, or function, words (articles, adjectives, adverbs, prepositions, and conjunctions). The hardest phrase for a Broca's aphasic to repeat is "No ifs, ands, or buts" (Geschwind, 1972).

Broca believed that expressive aphasia impaired motor instructions for vocalizing words. But Mr. Ford could recite the days of the week and the letters of the alphabet or sing "Home on the Range." So vocalization is not lost, but the ability to translate thoughts into speech patterns is compromised. The problem is "upstream" from speech in the brain, so reading and writing are impaired as much as is speech. Comprehension is also impaired when the meaning depends on grammatical words. For example, the patient can answer questions such as "Does a stone float on water?" but not the question "If I say, 'The lion was killed by the tiger,' which animal is dead?" (H. Gardner, 1975).

Wernicke's Area

In **Wernicke's aphasia**, the person has difficulty understanding and producing spoken and written language. This is often called *receptive aphasia*, but that term is misleading because the same problems with understanding language also show up in producing it. For example, the person's speech is *fluent* (smooth and effortless) but meaningless. This is in sharp contrast to Broca's aphasia, which is nonfluent. A patient asked to describe a picture of two boys stealing cookies behind a woman's back said, "Mother is away here working her work to get her better, but when she's looking the two boys looking in the other part. She's working another time" (Geschwind, 1979). This meaningless speech is called *word salad*, for obvious reasons.

Because the speech of an individual with Wernicke's aphasia is articulate and has the proper rhythm, it sounds normal to the casual listener. One of the authors was knocking on the social worker's door at a nursing home, and he thought it was because his thoughts were elsewhere that he failed to understand one of the residents when she spoke. But then his "Pardon me" elicited "She's in the frim-fram," and he realized the problem was hers rather than his. He responded with a pleasantry, and she gave a classic word-salad reply. That began a long relationship of conversations, but the difference was that neither of us ever understood the other; another difference was that it did not matter, because she seemed strangely unaware that anything was amiss.

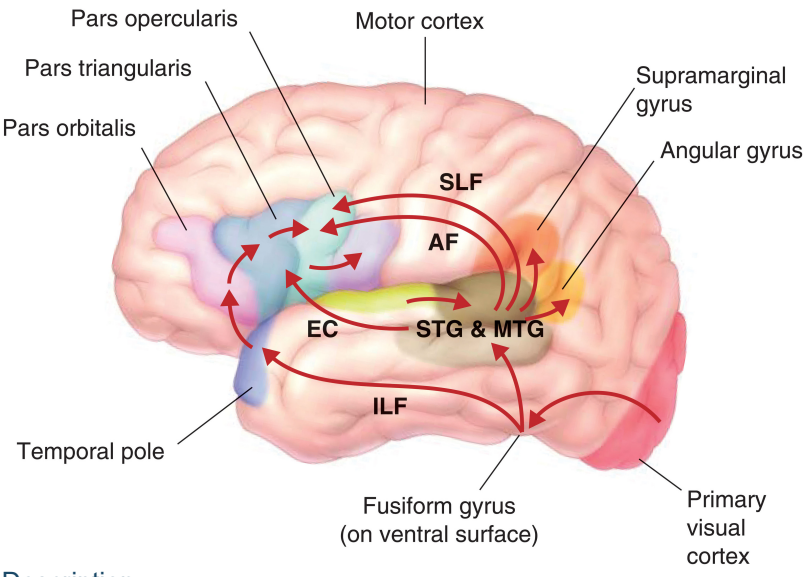
The Wernicke-Geschwind Model

Of course, language requires more than just these two areas. Wernicke suggested, and Norman Geschwind later elaborated on, a model for how Broca's area and Wernicke's area interact to produce language (Geschwind, 1970, 1972, 1979). The model is illustrated in Figure 9.18 and in the following examples. Answering a verbal question involves a progression of activity from the auditory cortex to Wernicke's area and then to Broca's area. Broca's area then formulates articulation of the verbal response and sends the result to the facial area of the motor cortex, which produces the spoken response. If the response is to be written, Wernicke's area sends output to the angular gyrus instead, where it elicits visual and motor patterns. When a person reads aloud, the visual information is translated into an auditory form by the angular gyrus and then passed to Wernicke's area, where a response is generated and sent to Broca's area to produce speech. The idea that visual information must be converted to an auditory form for processing arose in part from the fact that language evolved long before writing was invented, and Wernicke's area was believed to operate in an auditory fashion.

Beyond the Wernicke-Geschwind Theory

The Wernicke-Geschwind system has long been the primary model for how we understand language processing. Modern imaging techniques have confirmed the participation of Broca's and Wernicke's areas in language, and a study traced the progression of activity from the visual cortex to Wernicke's area and then to Broca's area as volunteers produced a verbal response to written material (Dhond, Buckner, Dale, Marinkovic, & Halgren, 2001). However, the Wernicke-Geschwind theory was developed as a model for single-word processing, largely based on case studies of individual patients; modern imaging techniques and more extensive investigation have shown that it is overly simplistic, with language engaging much broader areas of the brain. For example, damage to Broca's area alone does not cause Broca's aphasia, which requires damage to surrounding cortical areas and white matter underneath (Fujii et al., 2016). Noun use (naming objects) produces additional activity in the temporal lobe just below the auditory cortex and Wernicke's area (H. Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996). Verb use (describing what is happening in a picture) is impaired by damage to the left premotor cortex, which sends output to the motor cortex. This area is also activated while naming tools and by imagining body movements (Hauk, Johnsrude, & Pulvermüller, 2004); apparently when tool names are learned, they are stored near the brain structure that would produce the action.

Our understanding is still evolving, and at this point there is no agreement on a replacement for the classic model. However, what contemporary researchers are thinking is typified by the models proposed by Peter Hagoort (2016) and by Masazumi Fujii and his colleagues (2016). There are two major differences from the classic model. One is an increase in the number of language nodes; this is due in part to expanding Broca's and Wernicke's areas and dividing them into subregions, which have their own connections and make their own distinct contributions (Figure 9.19). In addition, we now have a second, parallel pathway connecting frontal with temporo-parietal language areas, as well as two additional pathways in the temporal lobe.



Description

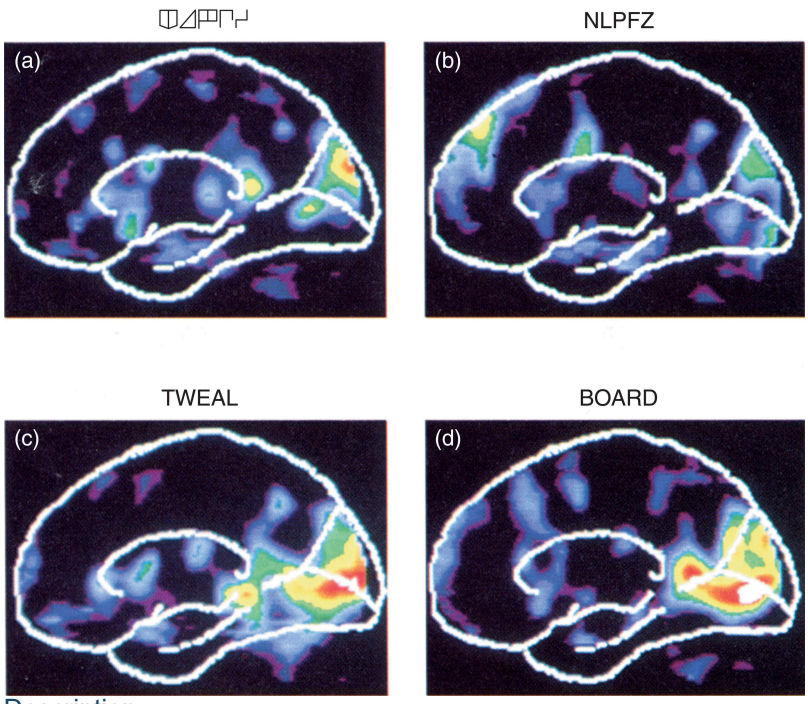
Figure 9.19 Beyond the Wernicke-Geschwind Model.
Contemporary models are similar to the Wernicke-Geschwind model, but with more structures and more pathways. AF = arcuate fasciculus; EC = extreme capsule; ILF = inferior longitudinal fasciculus; SLF = superior longitudinal fasciculus; STG & MTG = superior temporal gyrus and middle temporal gyrus.

Carolina Hrejsa/Body Scientific Intl.

The ventral stream of the language system connects regions involved in semantic processing (meaning). After spoken language is processed in the primary auditory cortex, it is converted into phonemes in the superior temporal gyrus; this series of phonemes is then transferred to the middle temporal gyrus, where they are recognized as words by comparing them with stored memories of words (Fujii et al., 2016). Further processing at the sentence level occurs in additional areas of the temporal lobe before the information is passed to the dorsal stream. There, the angular gyrus and supramarginal gyrus provide phonological (speech sounds) and syntactic (sentence structure) processing and send the result to the inferior frontal gyrus (location of Broca's area) for spoken or written expression. In the case of written language, the information passes from the visual cortex to the fusiform gyrus; this is the location of the visual word form area, which is involved in the identification of written words (Bouhali et al., 2014; L. Chen et al., 2019). The fusiform gyrus then sends the word information by the two routes shown in the figure to the frontal language areas.

Reading, Writing, and Their Impairments

Although aphasia affects reading and writing, these functions can be impaired independently of other language abilities when the visual inputs to the language network are interrupted. In language disorders, a complete absence of behavior has the prefix "a-," while impairment of behavior has the prefix "dys-." **Alexia** is the inability to read, and **agraphia** is the inability to write. Presumably, they are due to disruption of pathways through the **angular gyrus** that connect the visual projection area with the auditory and visual association areas in the temporal and parietal lobes (see Figures 9.18 and 9.19 again). The PET scans in Figure 9.20 show that activity increases in this area during reading.



Description

Figure 9.20 PET Scans During Reading.
Viewing letterlike forms (a) and strings of consonants (b) did not activate the area between the primary visual cortex and language areas, but reading pronounceable nonwords (c) and real words (d) did.

Source: From "Activation of Extrastriate and Frontal Cortical Areas by Visual Words and Word-Like Stimuli," S. E. Petersen, P. T. Fox, A. Z. Snyderand, and M. E. Raichle, *Science, 249*, pp. 1049–1044. Reprinted with permission from AAAS.

Reading and writing are also impaired in learning disorders. The most common learning disorders are **dyslexia**, an impairment of reading; *dysgraphia*, difficulty in writing; and *dyscalculia*, a disability with arithmetic. Because of its importance and the amount of research that has been done, we will focus on dyslexia. Dyslexia can be *acquired*, through damage, but its origin is more often *developmental*. Developmental dyslexia is partially genetic, with an estimated heritability between 40% and 60% (Gayán & Olson, 2001). Of the nine most reliably identified genes involved in dyslexia, four are involved in axon guidance and migration, and three contribute to cell functioning and dendrite formation (Mascheretti et al., 2017).

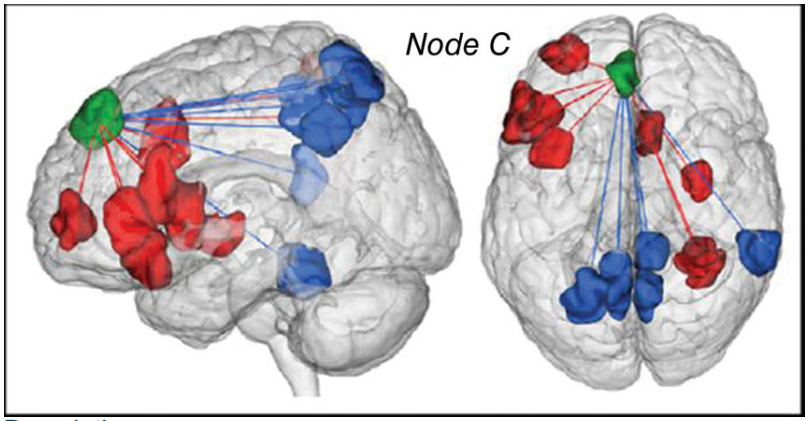
The impaired brain development manifests itself in three kinds of dyslexia symptoms: *phonological dyslexia*, which is difficulty connecting letters and words to the sounds they correspond to; *surface dyslexia*, inability to read words that are spelled differently from the way they're pronounced, such as yacht; and *rapid automatic naming dyslexia*, which is slowness in recognizing letter and numbers. Dyslexia was initially thought to be a visual-perceptual problem and in fact was originally called "congenital word blindness." This was based on symptoms such as reading words backward ("now" becomes "won"), confusing mirror-image letters (*p* and *q*, *b* and *d*), and trouble fixating on printed words, which seemed to move around on the page. These were sometimes attributed to processing speed issues that made it difficult to respond to handle the rapidly changing visual movements required in reading and to correct for normal unintentional eye movements, called saccades (Bucci, Bremond-Gignac, & Kapoula, 2008; M. S. Livingstone, Rosen, Drislane, & Galaburda, 1991).

However, since the 1970s, the predominant thinking has been that dyslexia is a not fundamentally a visual deficit but a language deficit (Castles & Friedmann, 2014). According to the **phonological hypothesis**, dyslexia is due to a disability in learning

grapheme-phoneme correspondences, that is, the correspondence between letters and their corresponding sounds of speech (Dehaene, 2009). According to this view, the speed issue is in tracking the rapid frequency and amplitude changes that distinguish speech sounds from each other (J. Stein, 2001); supposedly this impairs the dyslexic's ability to associate speech sounds with letters when learning to read. When a group of college students with dyslexia was administered a battery of tests, 10 had auditory deficits and 2 had a visual function deficit, but all 16 suffered from a phonological deficit (Ramus et al., 2003). Most researchers in the field now agree that phonological impairment is the cause of both reading impairment and at least some of the visual processing problems (Habib, 2000; Olulade, Napoliello, & Eden, 2013; but see Castles & Friedmann, 2014).

? What problems have been found in the brains of people with dyslexia?

Studies have consistently found structural and functional irregularities in the dyslexic brain. They found, for example, that the left planum temporale is smaller, to the point of being equal in size to the right. The **planum temporale**, which is the location of the posterior part of Wernicke's area, is typically about 13% larger in the left hemisphere than in the right, but it is equal in size in children with dyslexia (Bloom, Garcia-Barrera, Miller, Miller, & Hynd, 2013). Neural deficiencies appear early, and infants' neural responses to speech and pre-reading brain activity are related to risk for later development of dyslexia. Several studies have also found impaired structural connectivity across the white matter tracts that make up the reading network (González, Karipidis, & Tijms, 2018). A meta-analysis of PET and fMRI studies found reduced activity during reading-related tasks across most of the language network—in the left inferior frontal cortex (location of Broca's area), premotor and supramarginal cortices, and left inferior-temporal and fusiform regions (see Figure 9.19 again; Paulesu, Danelli, & Berlingeri, 2014). Some connections are atypically strong in adults with dyslexia, suggesting compensatory alterations. One of these is greater frontal connectivity with posterior brain areas than with left-hemisphere language areas (Figure 9.21). In addition, strong connection of the visual word form area (on the fusiform gyrus) with frontal areas involved in phonological analysis suggested reliance on "sounding out" words in lieu of a faster visual reading strategy (Finn et al., 2014).

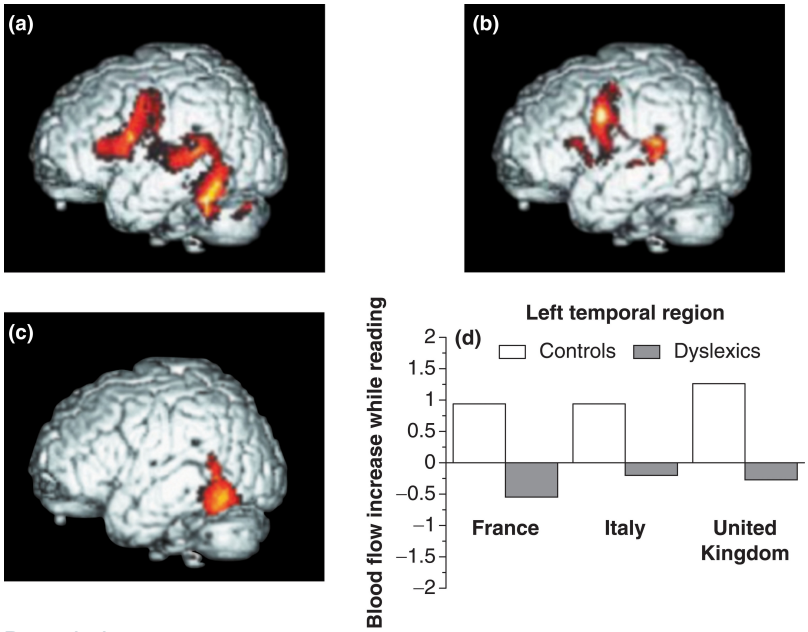


Description

Figure 9.21 Left- Versus Right-Hemisphere Language Processing in Nonimpaired and Dyslexic Readers.
Dyslexic readers have much less left hemisphere processing of language, compared to normal readers. Node C (green), an executive decision area in the frontal lobe, has strong connectivity with the language centers on the left side of the brain (red) in non-impaired readers. Dyslexic readers, in contrast, have stronger connections to bilateral posterior areas (blue).

Source: Figure 3C from "Disruption of Functional Networks in Dyslexia: A Whole-Brain, Data-Driven Analysis of Connectivity," by E. S. Finn, X. Shen et al., 2014, *Biological Psychiatry*, 76, pp. 397–404. With permission from Society of Biological Psychiatry.

Dyslexia occurs twice as often in some cultures as in others; this seems to suggest a cultural explanation for the disorder, but in fact the discrepancies support a brain-based phonological hypothesis. Italian and Spanish are phonologically simpler languages, with an almost one-to-one correspondence between phonemes and spelling. Predictably, dyslexia is much rarer in Italy and Spain than in French- and English-speaking countries, where the same spelling may have several pronunciations (*cough*, *tough*, *dough*, *slough*; can you guess the correct pronunciation for *Dr. Hough*?). PET imaging shows that Italians who are diagnosed with dyslexia have the same brain impairments seen in French and English speakers (Figure 9.22; Paulesu et al., 2001).



Description

Figure 9.22 Activation of Language Areas in Individuals With Dyslexia From Three Countries.
Here (a) shows activation due to reading in control subjects; (b) shows activation due to reading in individuals with dyslexia in all three countries; (c) indicates the area significantly more activated in controls during reading; and (d) shows that in all three countries, unimpaired individuals increase blood flow while reading, but those with dyslexia experience reduced flow.

Source: From "Dyslexia: Cultural Diversity and Biological Unity," by E. Paulesu, J.-F. Démonet, F. Fazio, E. McCrory, V. Chanoine, N. Brunswick, S. F. Cappa, G. Cossu, M. Habib, C. D. Frith, and U. Frith, *Science, 291*, pp. 2165–2167. Reprinted with permission from AAAS.

Recovery From Aphasia and Lateralization of Language

We have already mentioned that the left planum temporale averages 13% larger than the right; it also contains significantly more synapses, which apparently contributes to the left hemisphere's more efficient processing of speech (Ocklenburg et al., 2018). Damage to this and other critical left-hemisphere areas results in aphasia, varying in form and degree depending on the location and extent of injury. There is usually some recovery from acquired aphasia during the first 1 or 2 years, more so for Broca's aphasia than for Wernicke's aphasia (Martins & Ferro, 1992). Initial improvement is due to reduction of the swelling that often accompanies brain damage rather than to any neural reorganization. How the remaining recovery occurs is not well understood, but it is a testament to the brain's plasticity.

The right hemisphere can take over language functions following left-hemisphere damage, if the injury occurs early in life. A 2-year-old girl had a left-hemisphere stroke; her language was impaired, but she developed normal language capability by the age of 7. Then at the age of 56, she had a right-hemisphere stroke, which resulted in a second aphasia, from which she had only minimal recovery (Guerreiro, Castro-Caldas, & Martins, 1995). Right-hemisphere language control was confirmed by fMRI in all five individuals of a group who had been born with inadequate blood supply to the language areas of the left hemisphere (Vikingstad et al., 2000). Rasmussen and Milner (1977) used the *Wada technique* to determine the location of language control in patients before removing tissue that was causing epileptic seizures. The Wada technique involves anesthetizing one hemisphere at a time by injecting a drug into each carotid artery; when the injection is into the language-dominant hemisphere, language is impaired. Individuals whose left-hemisphere injury occurred before the age of 5 were more likely to have language control in the right hemisphere, supporting the hypothesis of right-hemisphere compensation. Patients whose left-hemisphere damage occurred later in life more often continued to have language control in the left hemisphere; there was, however, evidence in some cases that control had shifted into the border of the parietal lobe.

Because language functions are scattered widely in the left hemisphere, the compensation likely involves enhancing already existing activity rather than establishing new functional areas. The ability of the right hemisphere to assume language functions may result in part because it normally makes several contributions to language processing. The most obvious right-hemisphere role in language is **prosody**, the use of intonation, emphasis, and rhythm to convey meaning in speech. An example of one aspect of prosody is the *difference* between "You put the cat out when it's freezing" spoken as a statement and spoken as an emotion-filled question. We saw in Chapter 8 that people with right-hemisphere damage have trouble understanding emotion when it is indicated by speaking tone and in producing emotional speech the same way. An fMRI study found that right-hemisphere activity increased while individuals detected angry, happy, sad, or neutral emotions from the intonation of words (Buchanan et al., 2000). Some individuals with significant right hemisphere damage can still understand prosody, indicating that networks, rather than discrete brain areas, underlie this ability (Calvo et al., 2019).

The right hemisphere also is important in understanding information from language that is not specifically communicated by the meaning of the words, such as when the meaning must be inferred from context or when the meaning is figurative rather than literal. For example, interpreting the moral of a story activates the right hemisphere (Nichelli et al., 1995), as does understanding a metaphor or determining the plausibility of statements such as "Tim used feathers as paperweights" (Bottini et al., 1994). Interestingly, the right-hemisphere regions involved in all these activities correspond generally to the structures we have identified in left-hemisphere language processing.

A Language-Generating Mechanism?

When Darwin suggested that we have an instinctive tendency to speak, what he meant was that infants seem very ready to engage in language and can learn it with minimal instruction. Children learn language with such alacrity that by the age of 6, they understand about 13,000 words, and by the time they graduate from high school, their working vocabulary is at least 60,000 words (Kuhl & Damasio, 2013). This means that children learn a new word about every 90 waking minutes. The hearing children of deaf parents pick up language just about as fast as children with hearing parents (Lenneberg, 1969), despite minimal learning opportunities. Not only are preadolescent children particularly sensitive language learners; they are also believed to be the driving force in the development of creole language (which combines elements of two languages, allowing communication between the cultures). In Nicaragua, children in the school for the deaf, where sign language is not taught, have devised their own sign language with unique gestures and grammar (Senghas, Kita, & Özyürek, 2004).

Noam Chomsky (1980) and later Steven Pinker (1994) interpreted children's readiness to learn language as evidence of a **language acquisition device**, a hypothesized part of the brain dedicated to learning and controlling language. Not all researchers agree with this idea (see below), but most accept that there are biological reasons why language acquisition is so easy. This ease cuts across forms of language. For example, both hearing and deaf infants of signing parents babble in hand movements (Figure 9.23); the deaf infants' babbling proceeds into signing through the same stages and at about the same pace that children of speaking parents learn vocal language (Petitto, Holowka, Sergio, & Ostry, 2001; Petitto & Marentette, 1991). The researchers suggest that the ease of children's language acquisition is due to a brain-based sensitivity to rhythmic language patterns, a sensitivity that does not depend on the form of the language. Rhythm problems in childhood appear to correlate to reading disorders as adults (K. W. Carr, White-Schwoch, Tierney, Strait, & Kraus, 2014). And new evidence suggests that when musicians improvise passages within a larger ensemble, they use language centers as if they are participating in a musical conversation with the group (Donnay, Rankin, Lopez-Gonzalez, Jiradejvong, & Limb, 2014).

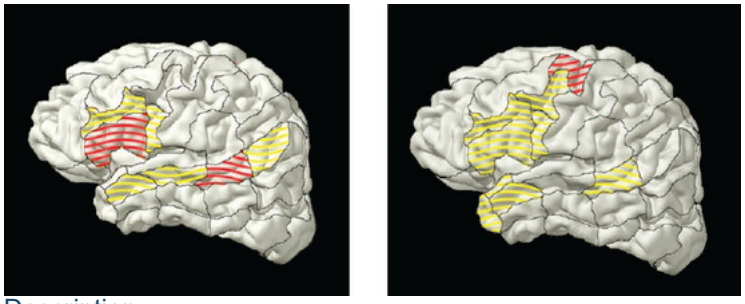
Figure 9.23 Babies of Signing Parents Babble With Their Hands.
Unlike the meaningless hand movements of other infants (which they also make at other times), their babbling is like their parents' signing. Babbling hand movements are slower and restricted to the space in front of the infants' bodies, and they correspond to the rhythmic patterning of adult sign-syllables.

Source: Petitto, Holowka, Sergio, & Ostry, "Language Rhythms in Baby Hand Movements." *Nature*, 413, 35–36. Photo courtesy of Dr. Laura-Ann Petitto, University of Toronto.

Innate Brain Specializations

More than 90% of right-handed people are left-hemisphere dominant for language. This is also true for two thirds to three fourths of left-handers; the remainder is about equally divided between right-hemisphere dominant and mixed (Knecht et al., 2000; B. Milner, 1974). In the large majority of autopsied brains, the left-hemisphere Broca's area is larger (Falzi, Perrone, & Vignolo, 1982), and the lateral fissure (Yeni-Komshian & Benson, 1976) and planum temporale (Geschwind & Levitsky, 1968; Rubens, 1977; Wada, Clarke, & Hamm, 1975) are longer. These differences are not the result of usage. By the 20th week of gestation, the left temporal lobe is already beginning to enlarge relative to the right (Kasprian et al., 2010), and the left planum temporale is larger by the 29th week (Wada et al., 1975). At birth or shortly after, speech causes a greater increase in cerebral blood flow than nonspeech sounds, speech sounds activate the same left-hemisphere language areas as in adults, and sentence melody activates the right hemisphere (reviewed by Friederici, 2006). Congenitally deaf individuals also have larger left temporal lobes, though the lack of auditory experience does result in fewer connections between language areas and auditory centers (Shibata, 2007).

Additional evidence for a language acquisition device comes from studies of individuals who communicate with sign language. Left-hemisphere damage impairs sign-language ability more than right-hemisphere damage does (Hickok, Bellugi, & Klima, 1996), and communicating in sign language activates the classical left-hemisphere language areas (Figure 9.24; Neville et al., 1998; Petitto et al., 2000). This was true of both congenitally deaf and normally hearing signers (all of whom had used sign language from infancy), but the finding is especially interesting in the deaf individuals, because it cannot be the result of the brain simply using pathways already established by an auditory language. It is also interesting because Wernicke's area was traditionally considered auditory in nature, which required the conversion of written words into an auditory form. Either the posterior language area is inherently more versatile than some theorists have thought, or the area underwent reorganization during infancy that enabled it to handle visual language. Either way, language seems to be a specialized capability of a limited subset of brain structures.



Description

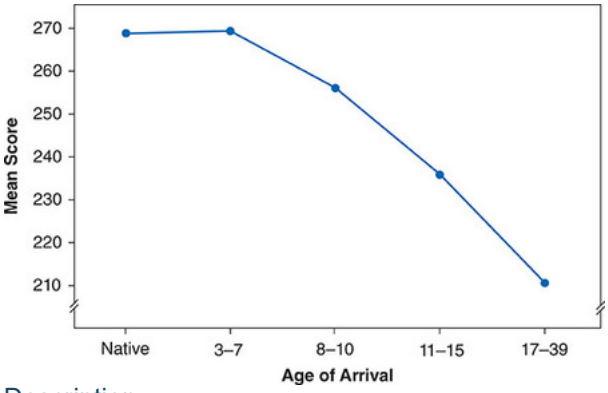
Figure 9.24 Language Areas in Hearing and Deaf Individuals.
(a) fMRI results while hearing subjects read written English. (b) Activation in subjects deaf from birth while processing sign language. Yellow areas were significantly activated and those in red more so.

Source: From "Cerebral Organizations for Language in Deaf and Hearing Subjects: Biological Constraints and Effects of Experience," by H. J. Neville et al., 1998, *Proceedings of the National Academy of Sciences, USA, 95*, pp. 922–929. © 1998 National Academy of Sciences, U.S.A.

Learning Multiple Languages

The ability to learn language is greatest during early childhood. A study of immigrants to the United States, for example, found that mastery of English declined dramatically beyond the age of 7 (Figure 9.25; J. S. Johnson & Newport, 1989). When children grow up in a bilingual home, the two languages are stored in the same location in the

brain; but if the second language is learned later in life when the brain is less plastic, imaging studies show that using the two languages activates nearby areas. The separation is so distinct, with centers of the areas as much as 4.5 to 9 mm apart, that damage can impair capability in one language while the other is unaffected (Figure 9.26; Gomez-Tortosa, Martin, Gaviria, Charbel, & Auman, 1995; K. H. S. Kim, Relkin, Lee, & Hirsch, 1997; M. S. Schwartz, 1994; Simos et al., 2001). A colleague of Lebanese descent told one of us that when his mother had a stroke, she lost her ability to speak and understand English. Her nearby relatives spoke no Lebanese, so when they needed to talk with her, they had to telephone a relative in another city to translate!



Description

Figure 9.25 The Critical Period of Language Acquisition.
Children can readily learn new languages when young, but they slowly lose this ability starting at puberty. The mean score is a relative measure of English mastery; the age of arrival is when the individual arrives in the United States and begins to learn English.

Source: From "Critical period effects in second language learning: the influence of maturational state on the acquisition of English as a second language," by J. S. Johnson & E. L. Newport, 1989, *Cognitive Psychology,* 21, pp. 60–99.

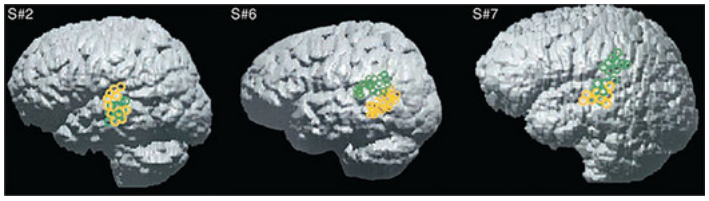


Figure 9.26 Brain Areas Activated by Different Languages in Bilingual Individuals.
Green circles represent areas activated by listening to English, and yellow circles indicate activation while listening to Spanish. These images are from different subjects, selected to represent the variability among 11 subjects. Although the patterns are different, in every case the languages activate separate areas.

Source: From "Mapping of Receptive Language Cortex in Bilingual Volunteers by Using Magnetic Source Imaging," by P. G. Simos, E. M. Castillo, J. M. Fletcher, D. J. Francis, F. Maestu, J. I. Breier, W. W. Maggio, & A.C. Papanicolaou, 2001, *Journal of Neurosurgery, 95,* pp. 76–81.

We still cannot say that language areas evolved specifically to serve language functions. You will see in the next section that some primates show similar enlargements in the left hemisphere, and their possession of language is questionable at best. A reasonable interpretation of these data is that certain brain areas evolved simply to handle rapidly changing information and complex discriminations, which language in its various forms requires. The strongest proponent of this "language as use" theory is Vyvyan Evans, who cites agrammatic languages in native Australia, as well as the lack of new spontaneous languages

forming in isolated groups of humans, as evidence that language may simply be the result of our vast capacity to learn. Another view is that the language areas are primarily specialized for different aspects of general learning: the frontal area for "procedural" or how-to learning that coincides with the rules of grammar and verb tenses and the temporal area for "declarative" or informational learning and, thus, the storage of word meanings and information about irregular word forms (Ullman, 2001). Even if these learning structures have been "borrowed" to serve language functions and the concept of a dedicated language acquisition device isn't meaningful, it is still clear that the human brain is uniquely well fitted for creating, refining, and learning language. We will explore the possible evolutionary roots of this ability in the context of animal language.

Language in Nonhuman Animals

Research has refuted most of humans' claims to uniqueness, including tool use, tool making, and self-recognition. Determining whether we have exclusive ownership of language has been more difficult. Animal language intrigues us, both because we're curious whether we have any company "at the top" and because we want to trace the evolutionary roots of language. Because language (like all behaviors) leaves no fossils behind, the origin of language is "a mystery with all the fingerprints wiped off" (Terrence Deacon, quoted by Holden, 2004a). Without this evidence, we are left with comparing the behavior and brains of our nonhuman relatives. The rationale behind animal language research is that any behavior or brain mechanism we share with other animals must have originated in common ancestors or through similar mechanisms. Although birds, dolphins, whales, and gorillas have been the subjects of language research, the major contenders for a coprocessor of language have been the chimpanzee and the bonobo. The reason is that humans and these ape species diverged from common ancestors a relatively recent 5 million years ago, and we still share 99% of our genetic material (Prufer et al., 2012).

A major obstacle has been deciding what we mean by *language*. Linguists agree that the vocalizations animals use to announce intentions or states (such as finding mates, detecting danger, and being hungry) are only signals and have little to do with language. Even the human toddler's request of "milk" may initially be just a learned signal to indicate hunger and, like the monkey's alarm call, indicate no language understanding. As you will see in the following discussion, some of the results obtained in language research with animals are equally difficult to interpret.

? What skills have chimps achieved in language studies?

A second hurdle was deciding how to communicate with chimpanzees. An early study that attempted to teach a home-reared chimpanzee (Viki) to talk failed because chimpanzees lack a larynx for forming words (Hayes & Hayes, 1953; Kellogg, 1968). Because chimpanzees normally communicate using gestures, later researchers turned to ASL with better success. Over a 4-year period, the chimpanzee Washoe learned to use 132 signs; she could request food or to be tickled or to play a game, and she would sign "sorry" when she bit someone (Fouts, Fouts, & Schoenfeld, 1984). And these gestures were transferrable to others: Washoe's adopted son, Loulis, learned 47 signs from her and three other chimps. The chimps regularly carried on sign-language conversations among themselves, most requesting hugs or tickling, asking to be chased, and signing "smile" (Fouts et al., 1984). But critics argued that no chimpanzee had learned to form a sentence; they concluded that expressions such as "banana me eat banana" are just a "running-on" of words, and Washoe's signing "water bird" in the presence of a swan was not the inventive characterization of "a bird that inhabits water" but the separate identification of the bird and the water it was on (Terrace, Petitto, Sanders, & Bever, 1979).

Results were more remarkable with bonobos, a near relative of chimpanzees and equally close to humans. When Duane and Sue Savage-Rumbaugh trained the bonobo Mutata to communicate by pressing symbols on a panel, her son Kanzi spontaneously began to communicate with the symbols and eventually learned 150 of them without any formal instruction (Figure 9.27; S. Savage-Rumbaugh, 1987; S. Savage-Rumbaugh, McDonald, Sevcik, Hopkins, & Rubert, 1986). Kanzi uses the

board to request specific food items or to be taken to specific locations on the 55-acre research preserve, asks one person to chase a specific other person, and responds to similar requests from trainers. His communication skills have been estimated at the level of a 2-year-old child (E. S. Savage-Rumbaugh et al., 1993).

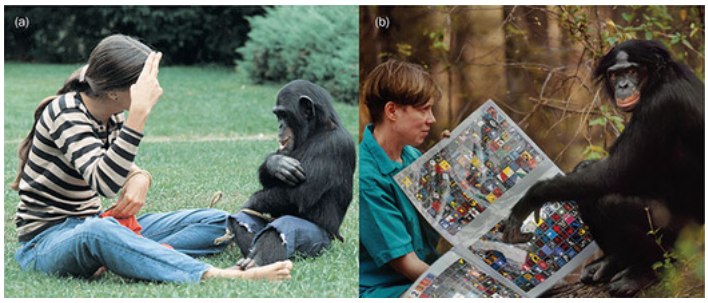


Figure 9.27 Language Research With Chimpanzees and Bonobos.
(a) A researcher converses with a chimp using American Sign Language. (b) A bonobo communicates through the symbol board.

Sources: (a) © Susan Kuklin/Science Source. (b) © Frans Lanting Studio/Alamy Stock Photo.

What about other, nonrelated animals? There is evidence that birds evolved a communication system with similarities to human language, even though birds and humans are evolutionarily separated by more than 350 million years. Even Charles Darwin, in his book *The Descent of Man and Selection in Relation to Sex* (1871), comments on the similarities between birdsong and human speech. Irene Pepperberg (1993) emphasized concept learning with her African gray parrot, Alex, but his communication skills turned out to be equally interesting. Using speech, Alex could tell his trainer how many items she was holding, the color of an item, or whether two items differed in shape or color. He also could respond to complex questions, such as “What shape is the green wood?” In addition, birds learn their songs in ways similar to how we learn language (see Marler, 1997, for a review); can have song dialects, just as humans have dialects (stable, geographically distinct language variations; Marler & Tamura, 1964; D. A. Nelson, 2000); can recall songs they’ve not used in years (G. E. Hough, Nelson, & Volman, 2000); and can even learn grammatical patterns like us (Gentner, Fenn, Margoliash, & Nusbaum, 2006). Some birds, such as the mockingbird, can even learn new “words” throughout adulthood and can control their vocal apparatus to mimic other species’ songs (Zollinger & Suthers, 2004).

So do we share language ability with animals? The behavior of animals such as Loulis, Kanzi, and Alex requires us to rethink our assumptions about human uniqueness, but no animal has yet turned in the critical language performance, and as far as we know, no animals in the wild have developed anything resembling a true language. But what some researchers do see in the animals’ performance is evidence of evolutionary foundations of our language abilities (Gannon, Holloway, Broadfield, & Braun, 1998).

Neural and Genetic Antecedents

An approach of some researchers has been to determine whether other animals share with us any of the brain organization associated with human language. The results have been intriguing. In the chimpanzee, as with humans, there is a greater ratio of white to gray matter in the left hemisphere than in the right (Cantalupo et al., 2009), and the left lateral fissure is longer and the planum temporale is larger (Gannon et al., 1998; Yeni-Komshian & Benson, 1976). Japanese macaque monkeys respond better to calls of their own species when the recorded calls are presented through headphones to the right ear (and, therefore, primarily to the left hemisphere) than when they are presented to the left ear. But there is no left-hemisphere advantage for the calls of another monkey species, which are non-meaningful (M. R. Petersen, Beecher, Zoloth, Moody, & Stebbins, 1978). Dolphins and the

Rumbaughs's chimps Austin and Sherman responded more quickly when symbols or command gestures were presented to their left hemisphere (Hopkins & Morris, 1993; Morrel-Samuels & Herman, 1993). Songbirds and parrots have language centers functionally analogous to Broca's and Wernicke's areas (called RA and HVC, respectively; Vu, Mazurek, & Kuo, 1994). Finally, birds also have a dominant side of the brain for controlling song: dominant-side lesions to HVC in both canary and zebra finch brains severely disrupted their songs (Nottebohm, 1977; H. Williams, Crane, Hale, Esposito, & Nottebohm, 1992).

? Do other animals share our brain structures for language?

Many researchers consider hand and face gestures to be more analogous to human speech than animal vocalizations are. They think that our ancestors communicated this way, aided in forming this simple but effective prelanguage by emerging language structures (Holden, 2004a; MacNeilage, 1998). Chimpanzees, our best living window into that ancestral past, communicate primarily through hand and face gestures (Figure 9.28; see A Further Look for more). Chimpanzees and baboons tend to favor the right hand when gesturing, suggesting a similar origin with our language (Meguerditchian & Vauclair, 2009; Meguerditchian, Vauclair, & Hopkins, 2010). These researchers believe that the ability to imitate gestures was critical to the development of language in humans; in fact, research indicates that children initially learn speech not by imitating sounds but by imitating the actions of the mouth (Goodell & Studdert-Kennedy, 1993), and the amount of gesturing at 14 months predicts vocabulary size at 54 months (Rowe & Goldin-Meadow, 2009). Now language theorists think they have identified the mechanism for the imitative development of language in mirror neurons, which you learned about in Chapter 8.

Figure 9.28 A Chimpanzee Communicating With Face and Hand Gestures.

Avalon /Contributor /Getty Images

A Further Look:

What Do the Gestures of Apes and Humans Have in Common?

A broadly accepted hypothesis among language researchers is that human language evolved out of our ancestors' communicative gestures. Because we have no records of primitive pre-language, we must resort to comparisons with our closest relatives, the great apes. Human communication involves inherited species-wide traits, such as grammar similarities and a shared repertoire of phonemes in early infancy; by analogy, we might expect similarities among the great apes in their use of gestures. In fact, chimpanzees share 60% of their gestures with gorillas, 80% with orangutans, and 90% with their nearer relatives, the bonobos. A comparison of gestures by chimps and bonobos showed that they overlapped extensively in meaning (K. E. Graham, Hobaiter, Ounsley, Furuichi, & Byrne, 2018). You can see videos of 70 gestures shared by most of the great apes at *The Great Ape Dictionary* (http://greatapedictionary.ac.uk/video-resources/gesture-videos). And both chimps and baboons (another closely related species of ape) tend to sign with their right hands, suggesting a left-hemisphere control of gestural language, just like most humans.

But what does this tell us about human language? There is no direct evidence, of course, but one third of the hand gestures used by chimpanzees in the wild are like those used by humans, such as beckoning to an individual or waving an individual away (Roberts, Vick, Roberts, Buchanan-Smith, & Zuberbühler, 2012). Unfortunately, human observation techniques are usually not as rigorous as those used with apes, which makes comparisons difficult to interpret. Researchers have now for the first time applied the same rigor in a study of 1- to 2-year-old children (Kersken, Gómez, Liszkowski, Soldati, & Hobaiter, 2019). Observations required identifying a target of the gesture; the gesture's goal (indicated by a response from the recipient that terminated the gesturing); and the gesture's meaning, indicated by achieving the same goal in multiple instances. The procedure produced 52 distinct gestures, 46 (88%) of which are seen in chimps. Although some of the gestures appeared to have the same meaning for children and the apes, there weren't enough data to answer that question; that will have to wait for a larger research effort.

Mirror neurons were first discovered in monkeys in the ventral premotor area corresponding to Broca's area in humans; they respond not only to monkeys' hand movements but also to communicative mouth gestures, such as lip smacking (Ferrari, Gallese, Rizzolatti, & Fogassi, 2003). In humans, mirror neurons have been found in the same area and in the superior temporal gyrus (location of Wernicke's area) and in the parietal lobe (Grèzes, Armony, Rowe, & Passingham, 2003; Holden, 2004a). Human mirror neurons are most active during imitation of another's movement (Iacoboni et al., 1999), which has encouraged the belief that they figure prominently in imitative ability and, thus, in the evolution of language (Figure 9.29). However, the fact that we share mirror neurons with monkeys and chimpanzees does not imply that monkeys and chimpanzees also share our language abilities. In fact, the evolutionary clues we do have suggest that while primitive gestural communication existed in early primates (Arbib, 2005), language developed well after the split that led to humans and chimpanzees (Holden, 2004a). In addition, the involvement of songbird HVC neurons in both the perception and the production of song is highly analogous to mirror neurons in human language centers (Bolhuis, Okanoya, & Scharff, 2010; Prather, Peters, Nowicki, & Mooney, 2008), suggesting that any species with mirror neurons may be capable of eventually evolving some form of language. Whatever brain foundations of language we share with other animals required extensive refinement, such as expansion of the brain, including the language areas; migration of the larynx lower in the throat, which increased vocalization range; and the development of imitative ability, which is poor in nonhuman primates (Holden, 2004a).

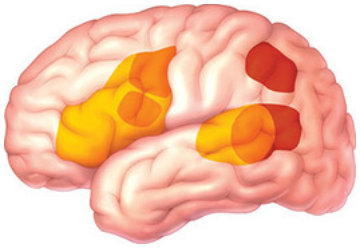


Figure 9.29 Overlap Between Language Areas and Areas Involved in Imitation. Yellow indicates Broca's and Wernicke's areas and nearby areas that are active during imitation of acts by others. The overlapping orange areas are also active, and red indicates additional areas involved in imitation.

Source: Image provided courtesy of Dr. Marco Iacoboni. Adapted from "The Origin of Speech," by C. Holden, 2004, *Science*, 303, p. 1318.

Suggesting that language is a product of evolution means, of course, that genes are involved. *KIAA0319*, one of the genes contributing to dyslexia, also plays a role in the development of speech and language (M. L. Rice, Smith, & Gayán, 2009), and *CNTNAP2* and *ATP2C2* have been implicated in language impairment (Newbury, Fisher, & Monaco, 2010; Vernes et al., 2008). *ROBO1*, a gene that controls axon guidance in fetal speech and hearing areas (C. Johnson, Drgon, McMahon, & Uhl, 2009), has been implicated in a particularly severe type of dyslexia (Hannula-Jouppi et al., 2005) and is also found in avian brain areas involved in song learning (R. Wang

et al., 2014). But the most researched and best understood language gene is *FOXP2*. A mutation of this gene results in reduced gray matter in Broca's area, along with articulation difficulties, problems identifying basic speech sounds, grammatical difficulty, and trouble understanding sentences (Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001; Pinker, 2001; Vargha-Khadem, Gadian, Copp, & Mishkin, 2005). We also share this gene with chimpanzees, but the human version differs in two apparently very important amino acids. The human version has been found in Neanderthal remains (J. Krause et al., 2007), and other fossil and archaeological evidence suggests to some researchers that the Neanderthals had the capacity for language. According to the researchers, the Neanderthals' increased nerve supply (assessed from the size of the bony pathways) enabled the voluntary control of the tongue and respiratory muscles necessary for speech; their auditory system specialized them for sensitivity in the speech range; and the spread of complex tool designs implied the imitative ability involved in learning speech (Dediu & Levinson, 2013). Inserting the human form of *FOXP2* into mice increased dopamine activity in the striatum (an area involved in fine movements and memory) and improved their learning performance; the researchers suggest that this learning enhancement contributed to the development of language (Schreiweis et al., 2014).

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- In what ways is the Wernicke-Geschwind model correct? In what ways is it incorrect?
- What are the different roles of the left and right hemispheres in language (in most people)? (See Chapter 8 for part of the answer.)
- How are human language and non-human primate communication similar and different?

IN PERSPECTIVE

Our guess is that at the beginning of this chapter, you would have said that vision is the most important sense. Perhaps now you can appreciate why Helen Keller thought her deafness was a greater disability than her blindness. Hearing alerts us to danger, brings us music, and provides for the social interactions that bind humans together. Small wonder that during evolution, the body invested such resources in the intricate mechanisms of hearing.

Hearing has important adaptive functions with or without the benefit of language, but from our vantage point as language-endowed humans, it is easy to understand Hudspeth's (2013) claim that audition's most important role is in processing language. The person who is unable to talk is at a disadvantage; the person who is unable to understand and to express language is nearly helpless. No wonder we put so much research effort into understanding how language works.

Some of the most exciting directions taken by language research have involved attempts to communicate with our closest nonhuman relatives and to make sense of the chirps and warbles of birds. Whether these animals possess language capabilities depends on how we define language. It is interesting how the capabilities we consider most characteristic of being human—such as language and consciousness—are the hardest to define. As so often happens, studying our animal relatives, however distant they may be, helps us understand ourselves.

Chapter Summary

- Sensation requires a receptor that is specialized for the kind of stimulus. Beyond sensation, the brain carries out further analysis, called perception.

Hearing

- The auditory mechanism responds typically to airborne vibrations, which vary in frequency and intensity.
- Sounds are captured and amplified by the outer ear and transformed into neural impulses in the inner ear by the hair cells on the basilar membrane. The signal is then transmitted through the brain stem and the thalamus to the auditory cortex in each temporal lobe.
- Frequency discrimination depends mostly on the basilar membrane's differential vibration along its length to different frequencies, resulting in neurons from each location carrying frequency-specific information to the brain. At lower frequencies, neurons fire at the same rate as the sound's frequency; it is possible that intermediate frequencies are represented by neurons firing in volleys, though research has not indicated that the brain utilizes this information.
- Although the cochlea is specialized for responding to pure tones, the basilar membrane apparently performs a Fourier analysis on complex sounds, breaking down a sound into its component frequencies.
- When different sounds must be distinguished from each other, stimulation from the brain apparently adjusts the sensitivity of the hair cells to emphasize one sound at the expense of others. Selective attention also results in differential activity in areas of the cortex.
- Locating sounds helps us approach or avoid sound sources and to attend to them despite competition from other sounds.
- The brain has specialized circuitry for detecting the binaural cues of differences in intensity, timing, and phase at the two ears.

Language

- Researchers have identified two major language areas in the brain, with Broca's area involved with speech production and grammatical functions and Wernicke's area with comprehension.
- Damage in either of the two general areas produces expressive aphasia or receptive aphasia, respectively, and damage to connections with the visual cortex impairs reading and writing. Developmental dyslexia may involve planum temporale abnormalities, reduced activity in the posterior language area, or deficiencies in the auditory and visual pathways.
- Contemporary research indicates that language involves more brain locations and more pathways than the classic Wernicke-Geschwind model described.
- Although some animals have language-like brain structures and have been taught to communicate in simple ways, it is controversial whether they possess true language. Their study suggests some possible evolutionary antecedents of

language, including gesturing and mirror neurons. Several genes with language functions have been identified, the best known being a variant of *FOXP2*, which was shared by Neanderthals.

Study Resources

For Further Thought

- Write a modified Wernicke-Geschwind theory of language control, based on later evidence.
- Would you rather give up your hearing or your vision? Why?
- Make the argument that chimps possess language, though at a low level. Then argue the opposite: that their behavior does not rise to the level of language.
- Look up the various language-associated genes discussed in the chapter and investigate what happens to language when mutations occur in those genes.

Test Your Understanding

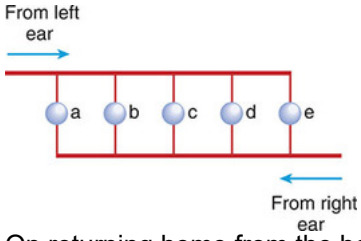
1. Describe the path of sound information from the outer ear to the auditory neurons, telling what happens at each point along the way.
2. State the telephone theory, the volley theory, and the place theory. Indicate a problem with each, and state the theory that is currently most widely accepted.
3. Summarize the Wernicke-Geschwind model of language function. Include structures, the effects of damage, and the steps in reading a word aloud and in repeating a word that is heard. Describe how contemporary thinking is different.

Select the best answer:

1. An adequate and an inadequate stimulus, such as light versus pressure on the eyeball, will produce similar experiences because
    1. they both activate visual receptors and the visual cortex.
    2. the receptors for touch and vision are similar.
    3. touch and vision receptors lie side by side in the eye.
    4. our ability to discriminate is poor.
2. Frequency is to pitch as
    1. loudness is to intensity.
    2. intensity is to loudness.
    3. stimulus is to response.
    4. response is to stimulus.
3. The sequence of sound travel in the inner ear is
    1. oval window, ossicles, basilar membrane, eardrum.
    2. ossicles, oval window, basilar membrane, eardrum.
    3. eardrum, ossicles, oval window, basilar membrane.
    4. eardrum, ossicles, basilar membrane, oval window.
4. Place analysis depends most on the physical characteristics of the
    1. hair cells.
    2. basilar membrane.
    3. tectorial membrane.
    4. cochlear canal.
5. The fact that neurons are limited in their rate of firing by the refractory period is most damaging to which theory?
    1. telephone
    2. volley
    3. place
    4. volley-place
6. The place theory’s greatest problem is that

1. neurons cannot fire as frequently as the highest-frequency sounds.
2. neurons specific for frequencies above 5000 Hz have not been found.
3. the entire basilar membrane vibrates about equally at low frequencies.
4. volleying does not follow sound frequencies above about 5000 Hz.

7. An auditory neuron's tuning curve tells you
   1. which frequency it responds to.
   2. which part of the basilar membrane the neuron comes from.
   3. at what rate the neuron can fire.
   4. how much the neuron responds to different frequencies.
8. A cochlear implant works because
   1. the tympanic membrane is intact.
   2. the hair cells are intact.
   3. it stimulates the auditory cortex directly.
   4. it stimulates auditory neurons.
9. An auditory object is
   1. a vibrating object in the environment.
   2. a sound recognized as distinct from others.
   3. the sound source the individual is paying attention to.
   4. None of the above
10. As a binaural sound location cue, difference in intensity works
    1. poorly at low frequencies.
    2. poorly at medium frequencies.
    3. poorly at high frequencies.
    4. about equally at all frequencies.
11. In the following diagram of coincidence detectors, which cell would respond most if the sound were directly to the person's left?



12. On returning home from the hospital, an elderly neighbor drags one foot when he walks and uses almost exclusively nouns and verbs in his brief sentences. You guess that he has had a mild stroke located in his
    1. left temporal lobe.
    2. right temporal lobe.
    3. left frontal lobe.
    4. right frontal lobe.
13. Most researchers agree that dyslexia is primarily a problem of
    1. development in Broca's area.
    2. development in the visual area.
    3. visual processing.
    4. phonological processing.
14. Evidence providing some support for a language acquisition device comes from studies showing that American Sign Language activates
    1. the left hemisphere.
    2. the left and right hemispheres.
    3. both frontal lobes.
    4. the occipital lobe.
15. The most reasonable conclusion regarding language in animals is that
    1. their signs amount to a primitive language.
    2. they can learn language to the level of a 6-year-old human.
    3. language is "built in" for humans but can be learned by animals.
    4. some animals have brain structures similar to human language structures.
16. The gene that has been most strongly linked to humans being able to acquire language is called
    1. *KIAA0319*
    2. *ROBO1*
    3. *ATP2C2*
    4. *FOXP2*

17. The role of mirror neurons in language development is supposedly in the
    1. imitation of word sounds.
    2. imitation of gestures and mouth actions.
    3. development of grammar.
    4. use of prosody.

Answers:

1. a, 2. b, 3. c, 4. b, 5. a, 6. c, 7. d, 8. d, 9. b, 10. a, 11. e, 12. c, 13. d, 14. a, 15. d, 16. d, 17. b.

For Further Reading

1. In *Auditory Neuroscience: Making Sense of Sound* (MIT Press, 2012), Israel Nelken and Andrew King draw on physics, psychophysics, and neuroscience to explain hearing, speech processing, sound localization, and auditory scene analysis. They end with a description of auditory prostheses.
2. *The Language Instinct* (Harper Perennial, 2007) is a reprint of Stephen Pinker's classic on the evolution of language. Pinker's expertise and lively writing style garnered one reviewer's evaluation as "an excellent book full of wit and wisdom and sound judgment."
3. *The Evolution of Social Communication in Primates* (Springer, 2014), edited by Marco Pina and Nathalie Gontier, is a fascinating series of articles about the origin of language in primates from philosophical, social, and evolutionary perspectives.
4. *Speaking American: How Y'all, Youse, and You Guys Talk: A Visual Guide*, by Joshua Katz (Houghton Mifflin Harcourt, 2016), is an excellent summary of the many regional language dialects in the United States and includes examples from specific cities nationwide.
5. "Genetics of Speech and Language Disorders," by Changsoo Kang and Dennis Drayna (*Annual Review of Genomics and Human Genetics*, 2011, *12,* 145–164), describes the progress made in identifying genes responsible for these disorders.
6. *"FOXP2*-Related Speech and Language Disorders," by Angela Morgan, Simon E. Fisher, Ingrid Scheffer, and Michael Hildebrand (*GeneReviews*, available at https://www.ncbi.nlm.nih.gov/books/NBK368474), describes the varied effects of *FOXP2* disruptions, ranging from speaking difficulties and loss of fine motor skills to decreased verbal IQ.

Key Terms

adequate stimulus 274

agraphia 295

alexia 295

angular gyrus 295

aphasia 292

auditory object 287

basilar membrane 278

Broca's aphasia 292

cochlea 274

cochlear canal 278

cocktail party effect 287

coincidence detectors 289

complex sound 276

dyslexia 295

Eustachian tube 278

frequency 275

frequency-place theory 284

frequency theory 281

grammar 291

head-related transfer function (HRTF) 288

inner hair cells 279

intensity 275

interaural level difference 288

interaural timing difference (ITD) 288

language 291

language acquisition device 299

loudness 275

organ of Corti 278

ossicles 278

outer hair cells 279

perception 274

phonological hypothesis 296

pinna 276

pitch 275

place theory 282

planum temporale 297

prosody 298

pure tone 276

receptor 274

sensation 274

tectorial membrane 278

telephone theory 281

tonotopically organized 279

tympanic membrane 278

volley theory 282

Wernicke's aphasia 293

Descriptions of Images and Figures

Back to Figure

A sound wave is represented as a sinusoidal wave. The height of the wave is labeled Amplitude and the length of one complete cycle is labeled Wavelength. An accompanying illustration shows diverging sound waves emerging from a speaker. The sound waves compress and decompress the air alternatingly. The region of the waves labeled Compression consists of more air molecules and the region of the waves labeled Decompression or rarefaction consists of fewer air molecules. Regions of compression correspond to the peak of the sinusoidal curve and regions of decompression correspond to the trough.

Back to Figure

1. A sinusoidal wave consisting of three tall peaks.
2. A sinusoidal wave consisting of three short peaks.
3. A sinusoidal wave consisting of five tall peaks.
4. A sinusoidal wave consisting of five short peaks.
5. A wave consisting of multiple peaks of different heights occurring at different intervals.
6. One cycle of the sound wave consists of a tall sharp peak, a short peak, and a peak of moderate height.

Back to Figure

The horizontal axis is labeled sound frequency in hertz, and ranges from 10 to 100,000. A red bar is between 1000 hertz and 4000 hertz. The vertical axis is labeled auditory threshold in decibels, and ranges from negative 10 to 60 in increments of 10. All data are approximate. The graph plots a line from (40, 60), passes through (100, 28) and (1000, 4) to (4000, negative 3), rises through (10,000, 30), and ends at (20,000, 60).

Back to Figure

1. Anatomy of ear: The external auditory canal from pinna ends at the tympanic membrane or eardrum. The hammer is in contact with the eardrum. The anvil is in contact with the hammer and the stirrup. The stirrup rests on the oval window, located adjacent to the round window on the cochlea, which leads to the three semicircular canals. The auditory nerve is attached to the cochlea.
2. Section of cochlea: A cross section of cochlea shows the vestibular canal, cochlear canal, and tympanic canal. A region adjacent to the cochlear canal is boxed.
3. Organ of Corti: A magnified view of the boxed region in the cross section of cochlea shows cochlear nerves leading to inner and outer hair cells under a layer of tectorial membrane. The hair cells rest on the basilar membrane.
4. Hair cells: Two probes, labeled neural impulses and receptor potential, are in contact with the hair cells. When the hair cells are upright, the rate of firing is normal at resting charge. When the hair cells move to the left, there is increased firing during depolarization. The hair cells are upright again. When the hair cells move to the right, there is decreased firing during hyperpolarization. An accompanying graph shows square peaks during depolarization and square troughs during hyperpolarization.

Back to Figure

The illustration shows the pathway through the left and right hemispheres of the brain. The flow diagram shows the pathways in the contralateral and ipsilateral sides.

The left hemisphere is the contralateral side, and the right hemisphere is the ipsilateral side. Auditory information from the cochlea passes through the auditory nerve that is surrounded by auditory nerve fibers from inner hair cells. The information reaches the cochlear nucleus in the brain stem of the right hemisphere. In the main pathway, the information from the cochlear nucleus travels along the left hemisphere of the brain. The information travels to the trapezoid body and superior olivary complex in the brain stem and through the lateral meniscus to the inferior colliculus in the midbrain. The information from trapezoid body travels to superior ovary complex, which then travels through the lateral meniscus to the inferior colliculus. From the inferior colliculus, the information reaches the medial geniculate body in the thalamus, and then to the auditory cortex. In the secondary pathway, the information from the cochlear nucleus travels along the right hemisphere of the brain. The information travels through superior olivary complex in the brain stem, inferior colliculus in the midbrain, medial geniculate body in the thalamus, and the auditory cortex. Inferior colliculus in both hemispheres of the brain are interconnected.
Back to Figure

The sound wave consists of 14 peaks. The responses by neurons are as follows.

Neuron 1 responds to first, fourth, seventh, eleventh, and fourteenth peaks.

Neuron 2 responds to first, fifth, eighth, and eleventh peaks.

Neuron 3 responds to second, fifth, ninth, and thirteenth peaks.

Neuron 4 responds to second, sixth, ninth, and twelfth peaks.

Neuron 5 responds to third, seventh, tenth, and thirteenth peaks.

The sum of responses of the neurons show responses to all peaks, with stronger response to first, second, fifth, seventh, ninth, eleventh, and thirteenth peaks.

Back to Figure

1. An illustration shows the cochlea. An accompanying illustration shows a spiral basilar membrane with a broad end in the middle and a narrow end at the outer tip. The frequency sensitivity of the membrane is 200 hertz in the middle and increases to 20000 hertz at the outer end.
2. An illustration of the brain shows primary and secondary auditory cortex in the temporal lobe. An arrow from the basilar membrane in illustration a points to the primary auditory cortex.
3. A graph plots sound intensity for different frequencies. The horizontal axis is labeled Frequency in hertz, and ranges from 100 to 10000. The vertical axis is labeled Sound intensity in decibels, and ranges from 0 to 90 in increments of 10. All data are approximate. The graph plots three curves. The first curve is plotted through (400, 60), (800, 15), and (2500, 78). The second curve is plotted through (2000, 60), (6000, 8), and (7000, 80). The third curve is plotted through (8500, 88), (20000, 20), and (30,000, 88). An arrow from the left side of the primary auditory cortex in illustration b points to 800 hertz along the horizontal axis, an arrow from the middle of the primary auditory cortex points to 6000 hertz, and an arrow from the right side of the cortex points to 20000 hertz.

Back to Figure

A coil placed on the surface of the skin close to the pinna receives input from microphone and sound processor. The receiver under the skin is connected to the coil. A wire from the receiver passes through the auditory canal, through the eardrum, and to the electrode in the cochlea.

Back to Figure

The waveform of clarinet consists of a tall and sharp peak, a sharp fall followed by three short peaks, a sharp fall followed by three more short peaks, and a sharp fall to a trough. The fundamental frequency is 0.5 kilohertz. The other frequencies range

from 1.0 to 9.5 kilohertz in increments of 0.5. With increase in frequency, the amplitude decreases.
Back to Figure

Sam receives high-frequency high-amplitude steady sound from an air conditioner unit, low-frequency high-amplitude irregular sound from Roger, high-frequency high-amplitude irregular sound from a music system, and low-frequency high-amplitude steady sound from a cat. The sound waves mix before reaching Sam. A thought bubble pointing toward Sam shows the air conditioner, Roger, the music system, and the cat.

Back to Figure

The sailor wears a frame that is strapped to his belt and consists of two rods extending along the shoulders. Forward-facing funnels are mounted on each rod. A tube is connected to each funnel, which is inserted into each ear.

Back to Figure

A listener, facing the speaker, is turned to his right, such that the left ear is closer to the speaker than the right ear. The distance between the horizontal lines extending between each ear is labeled interaural time difference and intensity difference. Diverging sound waves from the speaker pass through listener. The region of the wave between the listener's ears is labeled sound shadow.

Back to Figure

The circuit consists of five speakers, A through E, five coincidence detectors, A through E, and left and right ears. Speaker A is adjacent to the right ear, speaker B is close to the right ear, speaker C is between the right and left ears, speaker D is closer to the left ear, and speaker E is adjacent to the left ear. The coincidence detectors are arranged in a row in the following order from right ear to left ear: E, D, C, B, and A. The detectors are connected to each ear and the output.

Back to Figure

The illustration shows the following structures in each lobe:

- Broca's area and motor cortex consisting of facial motor area in the frontal lobe.
- Primary auditory cortex, Wernicke's area, and angular gyrus in the temporal lobe.
- Primary visual cortex in the occipital lobe.

Spoken input provided to the primary auditory cortex is sent to Wernicke's area. Written input provided to the primary visual cortex is sent to Wernicke's area through the angular gyrus. Signals from Wernicke's area passes through arcuate fasciculus and Broca's area to the facial motor area.

Back to Figure

The illustration shows the following structures in each lobe:

- Pars orbitalis, pars triangularis, and pars opercularis in the posterior side of the frontal lobe and facial motor area in inferior side of the motor cortex located in the posterior side of the frontal lobe.
- Temporal pole, primary auditory cortex, Wernicke's area, fusiform gyrus on the ventral surface, superior temporal gyrus, middle temporal gyrus, supramarginal gyrus, and angular gyrus in the temporal lobe.

- Primary visual cortex in the occipital lobe.

A signal starts from the primary auditory cortex and is sent to Wernicke's area, and then to pars opercularis through arcuate fasciculus and superior longitudinal fasciculus, supramarginal gyrus, and angular gyrus. Another signal from the primary visual cortex passes through the fusiform gyrus, temporal pole through inferior longitudinal fasciculus, pars orbitals, pars triangularis, and pars opercularis, and ends at the facial motor area. From the fusiform gyrus, the signal also passes through middle temporal gyrus and supramarginal gyrus, pars triangularis through extreme capsule, and pars opercularis, and ends at the facial motor area.
Back to Figure

1. A string of alphabet-like characters: The primary visual cortex shows mild activation.
2. A string of consonants N L P F Z: No activation.
3. A pronounceable nonword TWEAL: The primary visual cortex shows high activation.
4. Pronounceable word BOARD: The primary visual cortex shows very high activation.

Back to Figure

Node C is in the frontal lobe of the brain. In non-impaired readers, the node has strong connections with many areas in the frontal lobe in the left hemisphere and few areas in the parietal lobe in the right hemisphere. In dyslexic readers, the node has strong connections with many areas in the posterior side of the brain in both hemispheres.

Back to Figure

1. Posteroinferior side of the frontal lobe, primary visual cortex, Wernicke's area, and fusiform gyrus are activated.
2. Posteroinferior side of the frontal lobe and some regions of the visual cortex and Wernicke's area are activated.
3. Posteroinferior side of the temporal lobe is activated.
4. The horizontal axis lists countries. The vertical axis is labeled Blood flow increase while reading and ranges from negative 2 to 2 in increments of 0.5. The approximate data from the graph are tabulated below.

Back to Figure

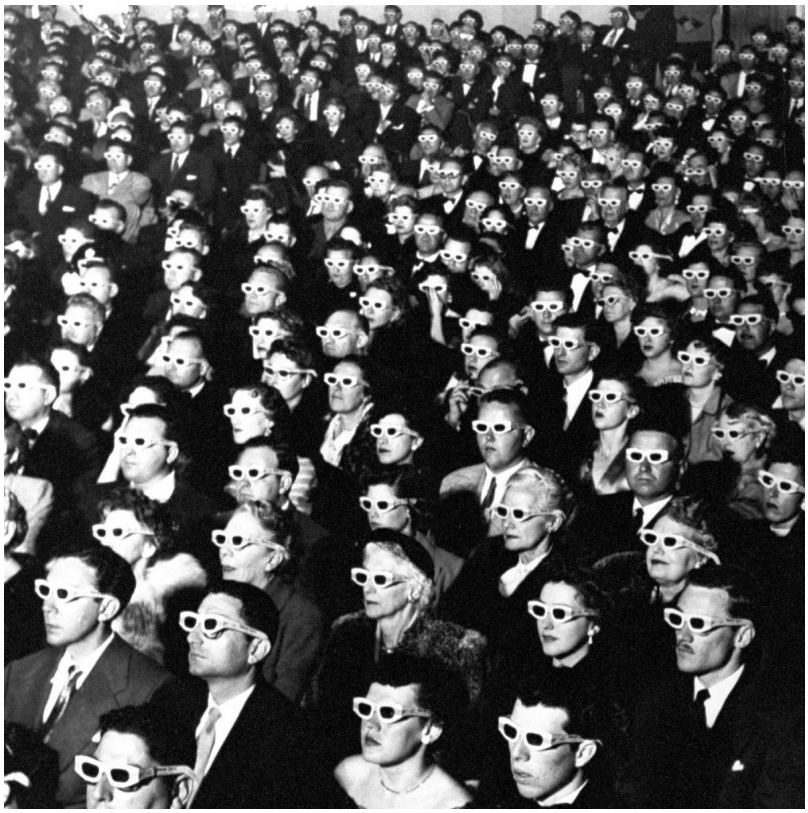
In the first scan, the central part of the frontal lobe, posterior part of the motor cortex, primary auditory cortex, supramarginal gyrus, and angular gyrus are more activated than the posteroinferior part of the frontal lobe and Wernicke's area.

In the second scan, the posterior part of the frontal lobe, anterior pat of the temporal lobe, and Wernicke's area are more activated than the superior region of the motor cortex.

Back to Figure

The horizontal axis is labeled age of arrival, and lists native and different age groups. The vertical axis is labeled mean score, and ranges from 210 to 270 in increments of 10. The approximate data from the graph are tabulated below.

10 VISION AND VISUAL PERCEPTION



J. R. Eyerman/The LIFE Picture Collection/Getty Images

Light and the Visual Apparatus

- The Visible Spectrum
- The Eye and Its Receptors
- Pathways to the Brain

Concept Check

Color Vision

- Trichromatic Theory
- Opponent Process Theory
- A Combined Theory

A Further Look | Restoring Lost Vision

Color Blindness

Concept Check

Form Vision

Contrast Enhancement and Edge Detection

A Further Look | Neural Bases of Visual Illusions

Hubel and Wiesel's Theory

Spatial Frequency Theory

Concept Check

The Perception of Objects, Color, and Movement

The Two Pathways of Visual Analysis

Disorders of Visual Perception

The Problem of Final Integration

Concept Check

A Further Look | When Binding Goes Too Far

In Perspective

Chapter Summary

Study Resources

After reading this chapter, you will be able to

10.1 Describe the functions of structures within the eye.

10.2 Illustrate the processing pathways of visual information from the eye up to cortical brain areas.

10.3 Compare the major theories of color processing.

10.4 Contrast the major theories of form processing.

10.5 Discuss how visual information is segregated and reconstructed in the visual system.

10.6 Identify how action potentials and synaptic transmission can produce a variety of visual experiences.

10.7 Predict how damage to specific portions of the visual system will impact a person's visual perceptions.

Jonathan I. was in his car when a small truck hit it. In the emergency room, he was told that he had a concussion. For a few days, he was unable to read, saying that the letters looked like Greek, but fortunately this alexia soon disappeared. Jonathan was a successful artist who had worked with the renowned Georgia O'Keeffe, and he was eager to return to his work. Driving to his studio, he noticed that everything appeared gray and misty, as if he were driving in a fog. When he arrived at his studio, he found that even his brilliantly colored paintings had become gray and lifeless.

His whole world changed. People's appearance was repulsive to him, because their skin appeared "rat colored"; he lost interest in sex with his wife for that reason. Food was unattractive, and he came to prefer black and white foods (coffee, rice, yogurt, black olives). His enjoyment of music was diminished, too; before the accident, he used to experience synesthesia, in which musical tones evoked a sensation of changing colors, and this pleasure disappeared as well. Even his migraine headaches, which had been accompanied by brilliantly colored geometric hallucinations, became "dull." He retained his vivid imagery, but it too was without color.

Over the next 2 years, Jonathan seemed to forget that color once existed, and his sorrow lifted. His wife no longer appeared rat colored, and they resumed sexual activity. He turned to drawing and sculpting and to painting dancers and race horses, rendered in black and white but characterized by movement, vitality, and sensuousness. However, he preferred the colorless world of darkness and would spend half the night wandering the streets (O. Sacks & Wasserman, 1987).

Vision enables us to read and to absorb large amounts of complex information. It helps us navigate in the world, build structures, and avoid danger. Color helps distinguish objects from their background, and it enriches our lives with natural beauty and works of art. We suspect that in contrast to Helen Keller's belief that deafness was a greater affliction than blindness, most of you would consider vision the most important of our senses. Apparently, researchers share that opinion, because vision has received more research attention than the other senses combined. Thus, we understand a great deal about how the brain processes visual information. In addition, studies of vision are providing a valuable model for understanding complex neural processing as well as consciousness itself.

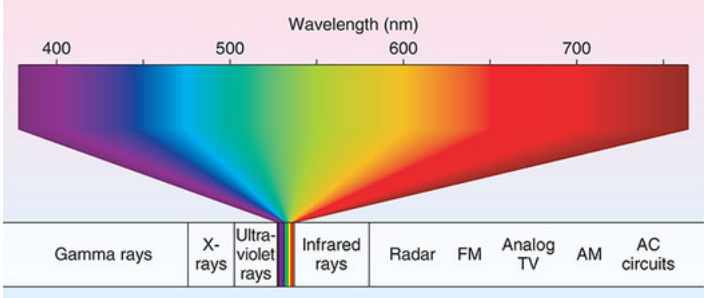
LIGHT AND THE VISUAL APPARATUS

Vision is an impressive capability. There are approximately 97 million light receptors in the human eye (Curcio, Sloan, Kalina, & Hendrickson, 1990), and a complex network of cells connecting them to each other and to the optic nerve. The optic nerve boasts about 1.2 million axons (Jonas, Schmidt, Müller-Bergh, Schlötzer-Schrehardt, & Naumann, 1992), compared with 30,000 in the auditory nerve. The high ratio of retinal receptors to optic nerve axons tells us that a great deal of processing goes on in the retina itself. The optic nerve transmits information to the brain at an estimated 100 million bits per second, comparable to Ethernet data transmission rates (K. Koch et al., 2006). What our brain does with the information it receives from the eye is equally remarkable. The topics of vision and visual perception form an exciting story, one of high-tech research and conflicting theories and dedicated scientists' lifelong struggles to understand our most amazing sense.

The Visible Spectrum

To understand vision, we need to start at the beginning by describing the *adequate stimulus*, as we did with audition. To say that the stimulus for vision is light seems obvious, but the point needs some elaboration. Visible light is a part of the

electromagnetic spectrum. The **electromagnetic spectrum** includes a variety of energy forms, ranging from gamma rays at one extreme of frequency to the radiations of alternating current circuits at the other (Figure 10.1); the portion of the electromagnetic spectrum that we can see is represented by the colored area in the figure.



Description

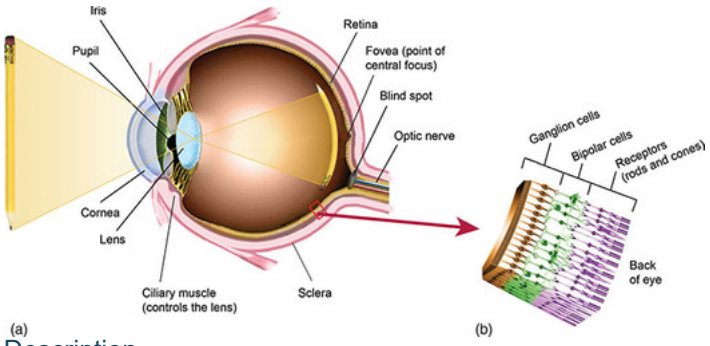
Figure 10.1 The Electromagnetic Spectrum.
The visible part of the spectrum is the middle (colored) area, which has been expanded to show the color experiences usually associated with the wavelengths. Only 0.0035% of the electromagnetic spectrum is visible to humans.

The visible part of the electromagnetic spectrum accounts for only 1/70 of the frequency range. Most of the frequencies are not useful for producing images; for instance, AM, FM, and analog television waves pass right through objects. Some of the other energy forms, such as X-rays and radar, can be used for producing images, but they require powerful energy sources and special equipment for detecting the images. Heat-producing objects give off infrared energy, which some nocturnal animals (such as the sidewinder rattlesnake) use to detect their prey in darkness. Humans can convert infrared images to visible ones with the aid of specialized equipment, and this capability is very useful to the military and law enforcement for detecting heat-producing individuals, heat-producing vehicles, and armament at night. Sometimes this ability can be used to deceive heat-detecting equipment; during the first Gulf War, the Iraqi army set up plywood silhouettes of tanks with heaters behind them to distract Allied airplanes. But infrared is best for detecting nearby objects—distant ones have blurred edges and fuzzy detail. The electromagnetic energy within our detectable (visible) range produces well-defined images because it is reflected from objects with minimal distortion. We are adapted to life in the daytime, and we sacrifice the ability to see in darkness in exchange for crisp, colorful images of faces and three-dimensional (3-D) objects in daylight. In other words, our sensory equipment is adapted for detecting the energy that is most useful to us, just as the night-hunting sidewinder rattlesnake is equipped to detect the infrared radiation emitted by its prey and a bat's ears are specialized for the high-frequency sound waves it bounces off small insects.

Light is a form of oscillating energy and travels in waves just as sounds do. We could specify visible light (and the rest of the electromagnetic spectrum) in terms of frequency, just as we did with sound energy, but the numbers would be extremely large. So we describe light in terms of its wavelength—the distance the oscillating energy travels in one complete cycle. (We could do the same with sound, but those numbers would be just as inconveniently small.) The unit of wavelength is the nanometer (nm), which is a billionth of a meter; visible light ranges from about 380 to 800 nm. Notice in Figure 10.1 that different wavelengths correspond to different colors of light; for example, when light in the range of 500 to 570 nm strikes the receptors in our eye, we normally report seeing green. Later in the chapter, we will qualify this relationship when we examine why wavelength does not always correspond to the color we see (just like our pitch perception isn't perfectly aligned with sound frequency).

The Eye and Its Receptors

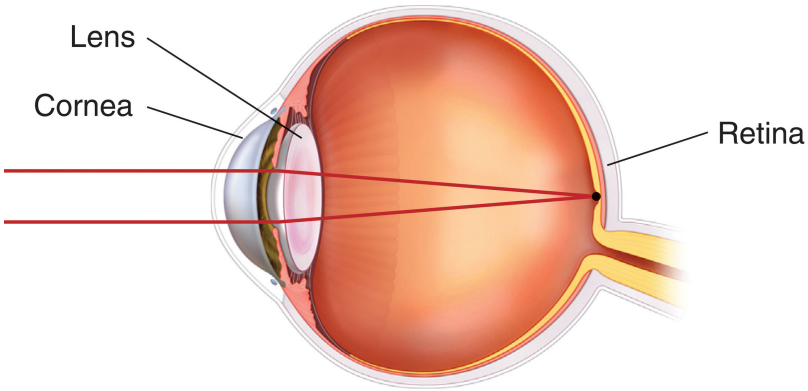
The eye is a spherically shaped structure filled with a clear, thick liquid (Figure 10.2a). The white outer covering, or sclera, is opaque except for the cornea, which is transparent. Behind the cornea is the iris, which gives your eye its color. The iris is a circular muscle that controls the amount of light entering your eye by contracting reflexively in bright light and relaxing in dim light. You can observe this response in yourself by watching in a mirror while you change the level of light in the room. The pupil is not a structure but simply an opening surrounded by the iris muscle; it looks black because light that enters your eye is absorbed by the retina and isn't reflected out. Behind the iris is the lens. Notice in the figure that the lens projects the image upside down and backward onto the retina. You can demonstrate this by touching the side of your eye through your closed lid—you'll be manually stimulating the retina on one side, but you'll see a flashing spot on the other side of your eye—if you move your finger down, the spot moves up. Because the normally flat lens is a remarkably flexible tissue, the ciliary muscles attached to it can contract to make the lens rounder to focus on a near object through a process called **accommodation** (Figure 10.3).



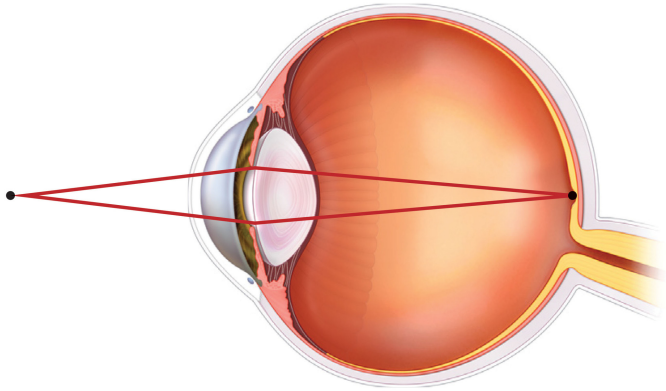
Description

Figure 10.2 The Human Eye and Retina.
In (a), the major parts of the eye are shown. In (b), the major pathway of visual information is shown (photoreceptor to bipolar cells to ganglion cells). (Note how the connections to the cones "fan out" away from the fovea, making the cones there more accessible to light.)

Source: Modified from Figure 26-1 in Eric R. Kandel, James H. Schwartz, Thomas M. Jessell, Steven A. Siegelbaum, & A. J. Hudspeth. *Principles of Neural Science* (5th Edition), 2013.



(a) Object far—eye relaxed



(b) Object near—eye accommodation
Description

Figure 10.3 Accommodation of the Lens.
When you are looking at something far away, the muscles surrounding the lens relax, and the lens flattens (a). When you focus on something close, the muscles contract and make the lens more round. This is called accommodation (b).

Source: Schwartz, B. L. & Krantz, J. H. (2015).

The **retina**, the light-sensitive tissue at the rear of the eye, is made up of two main types of light-sensitive receptor cells, called rods and cones, and the neural cells connected to them. As you can see in Figure 10.4, the receptors—collectively referred to as *photoreceptors*—are at the very back of the eye. The photoreceptors connect to *bipolar cells*, which in turn connect to *ganglion cells*, whose axons form the optic nerve. Notice that light must pass through the bipolar and ganglion cells to reach the photoreceptors; the neural cells are very small and transparent, though, so they block very little light (see Figure 10.2b). The photoreceptors are filled with light-sensitive chemicals called **photopigments**. The photopigment absorbs energy from the light that causes some of the molecules to break down into two components, and the ensuing chemical reaction ultimately results in a neural response. The two components then recombine to maintain the supply of photopigment.

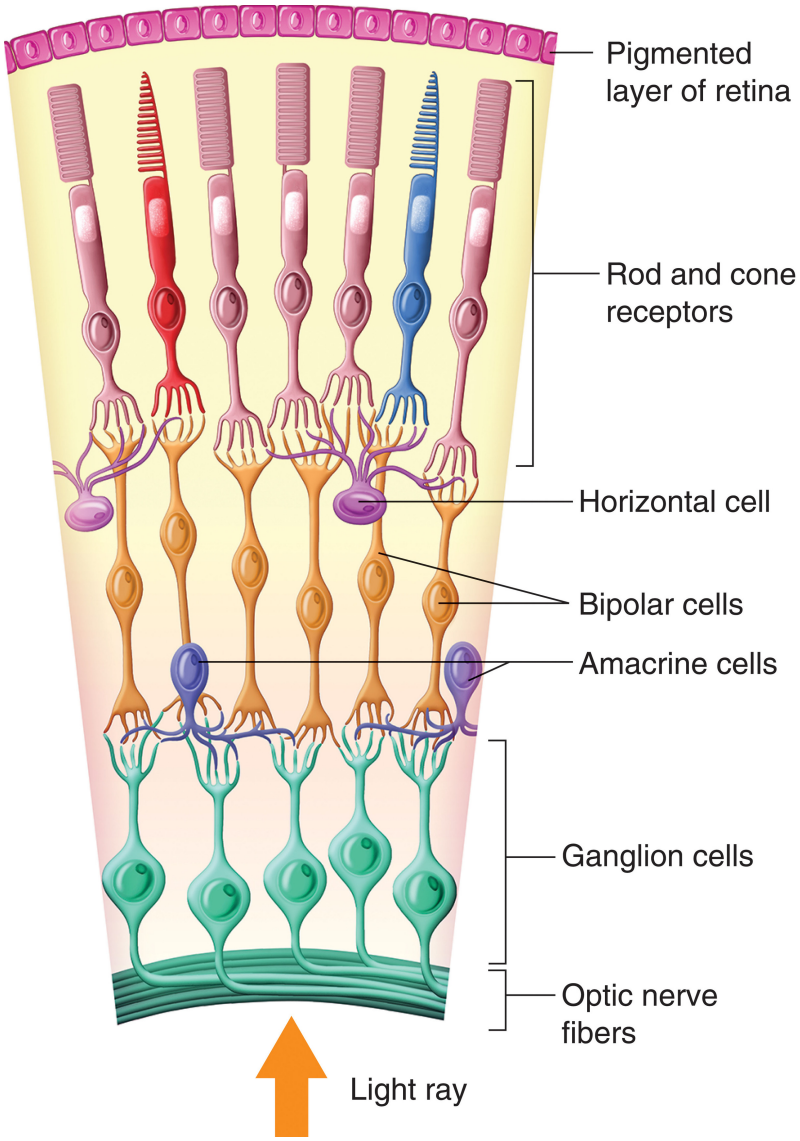


Figure 10.4 The Cells of the Retina.

Source: Adapted from "Organization of the Primate Retina," by J. E. Dowling and B. B. Boycott, *Proceedings of the Royal Society of London, B166,* Fig. 23 on p. 104. Copyright 1966 by the Royal Society.

The rods and cones are named for their shapes, as you can see by looking at Figure 10.4 again. The human eye contains about 92 million rods and about 4.6 million cones (Curcio et al., 1990). The two types of receptors contain different kinds of photopigments; rods and cones function similarly, but their chemical contents and their neural connections give them different specializations.

? How does the eye detect light?

The rod photopigment is called **rhodopsin**; the name refers to its color (from the Latin *rhodon*, "rose"), not to its location in rods. Rhodopsin absorbs light much faster than cone photopigment, so it is used exclusively for low-light situations. In very bright light, the rhodopsin in your eyes remains broken down most of the time, so the rods are not useful. The brief delay in adjusting to a darkened movie theater is due to the time it takes the rhodopsin to resynthesize. **Iodopsin**, the cone photopigment,

requires a high light intensity level, so your cones function well in daylight but are nonfunctional in dark situations. Three varieties of iodopsin, located in different cone types, respond best to different wavelengths of light; this means that cones detect only certain different wavelengths, whereas rods differentiate only among different levels of light and dark (which is why you cannot recognize colors in dim light).

Rods and cones also differ in their retinal distribution and in their amount of neural interconnection. Cones are most concentrated in the **fovea**, a 1.5-millimeter-diameter circle in the middle of the retina, and drop off rapidly with distance from that point. Rods are most concentrated at 20 degrees from the fovea; from that point, they decrease in number in all directions and fall to zero in the fovea. In the center of the fovea, one cone synapses on a single bipolar cell, which synapses on a single ganglion cell (Masland, 2017); the number of cones per ganglion cell increases with distance from the center but remains small compared with rods. Because few cones share ganglion cells, the fovea has higher **visual acuity**, or ability to distinguish details. Acuity gets a further boost at the fovea because the connecting cells are pushed to the side, eliminating the slight scattering of light that occurs in the rest of the retina. In contrast to cones, many rods share a single ganglion cell; this reduces their resolution but enhances their already greater sensitivity to dim light. The area of the retina from which a ganglion cell (or any other cell in the visual system) receives its input is the cell's **receptive field**. So we can say that receptive fields are smaller in the fovea and larger in the periphery. Table 10.1 summarizes the characteristics of these two visual systems.

Table 10.1

TABLE 10.1 Summary of the Characteristics of the Rod and Cone Systems.

	ROD SYSTEM	CONE SYSTEM
Function	Functions best in dim light, poorly or not at all in bright light.	Functions best in bright light, poorly or not at all in dim light.
	Detail vision is poor.	Detail vision is good.
	Does not distinguish colors.	Subset distinguishes among colors.
Location	Mostly in periphery of retina.	Mostly in fovea and surrounding area.
Receptive field	Large, due to convergence on ganglion cells; contributes to light sensitivity.	Small, with one or a few cones converging on a single ganglion cell; contributes to detail vision.

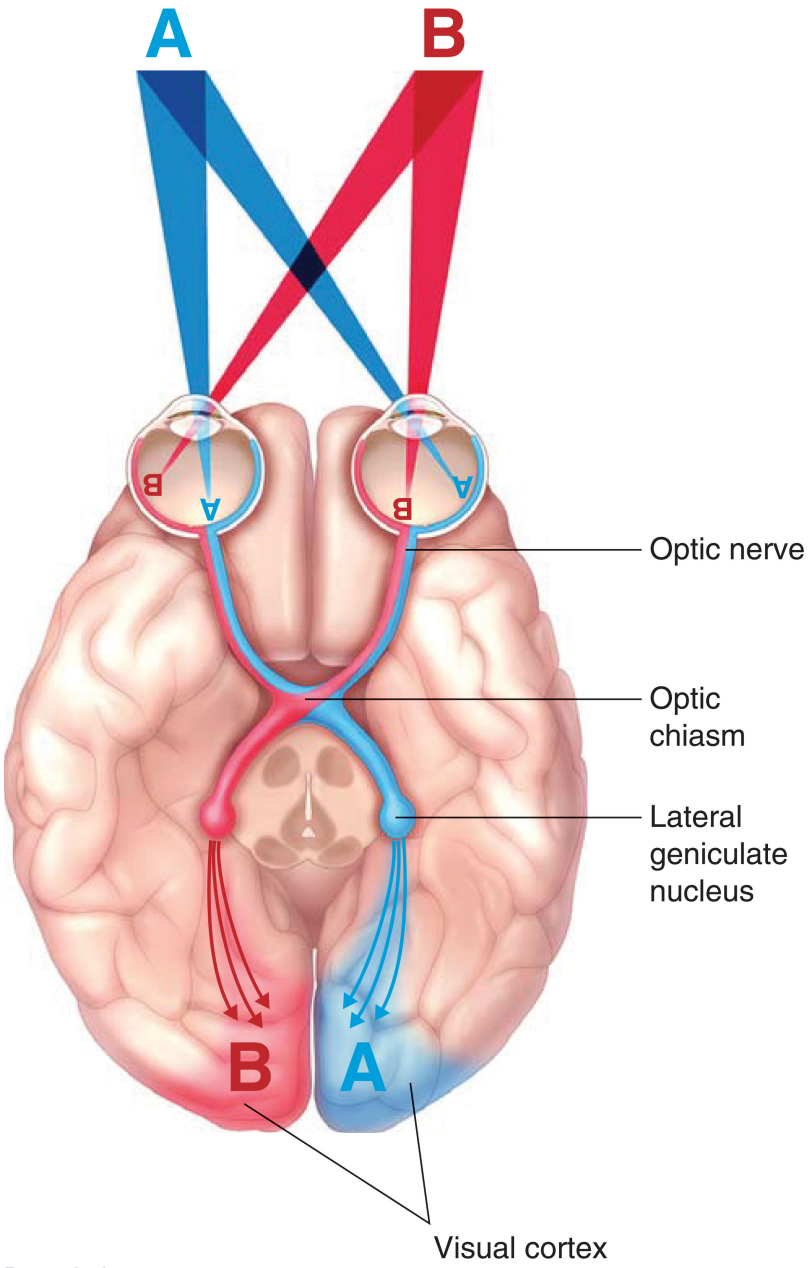
The receptors' response to light is different from what you might expect, because they are most active when they are *not* being stimulated by light. In darkness, the photoreceptor's sodium and calcium channels are open, allowing these ions to flow in freely. Thus, the membrane is partially depolarized; the receptor releases a continuous flow of glutamate, and this *inhibits* activity in the bipolar cells. The chemical response that occurs when light strikes the photopigments closes the sodium and calcium channels, reducing the release of glutamate in proportion to the amount of light. The bipolar cells release more neurotransmitters, which increases the firing rate in the ganglion cells. (The photoreceptors and bipolar cells do not produce action potentials.) In neural terms, ganglion cells undergo what is called "release from inhibition."

If you look again at Figure 10.4, you can see that the rods and cones are highly interconnected by *horizontal cells*. In addition, *amacrine cells* connect across many ganglion cells. All this interconnection might suggest to you that the retina does more than transmit information about points of light to the brain. Along with the high ratio of receptors to ganglion cells, this is a second indication that considerable processing occurs before the signal leaves the retina. You will soon see evidence that this is true. With such complexity, it's no wonder most vision scientists consider the retina to be part of the brain and refer to the optic nerve as a tract!

Pathways to the Brain

The axons of the ganglion cells join and pass out of each eye to form the two optic nerves (Figure 10.5). Where the nerve exits the eye, there are no receptors, so it is referred to as the *blind spot* (see Figure 10.2a). This point is located about 20 degrees toward the outside and down slightly from the usual focal point of each retina. The blind spots of the two eyes fall at different points in a visual scene, so you do not notice that any of your visual world is missing; besides, your brain is good at "filling in" missing information, even when a small part of the visual system is

damaged. The two optic nerves run to a point just in front of the pituitary gland, where they join for a short distance at the *optic chiasm* before separating again and traveling to their first synapse in the *lateral geniculate nuclei* of the thalamus. At the optic chiasm, axons from the nasal sides of the eyes cross to the other side and go to the occipital lobe in the opposite hemisphere. Neurons from the outside half of each eye (the temporal side) do not cross over but go to the same side of the brain.



Description

Figure 10.5 Projections From the Retinas to the Cerebral Hemispheres. Notice how images of objects in the left and right sides of the visual field fall on the opposite sides of the two retinas; the information from the two eyes then travels to the visual cortex in the hemisphere opposite the object, where it is combined. (The distance between the two lateral geniculate nuclei is greatly exaggerated.). The inset demonstrates the separation of information from each eye into separate ocular dominance columns (white from left eye, gray from right eye).

Carolina Hrejsa/Body Scientific Intl.

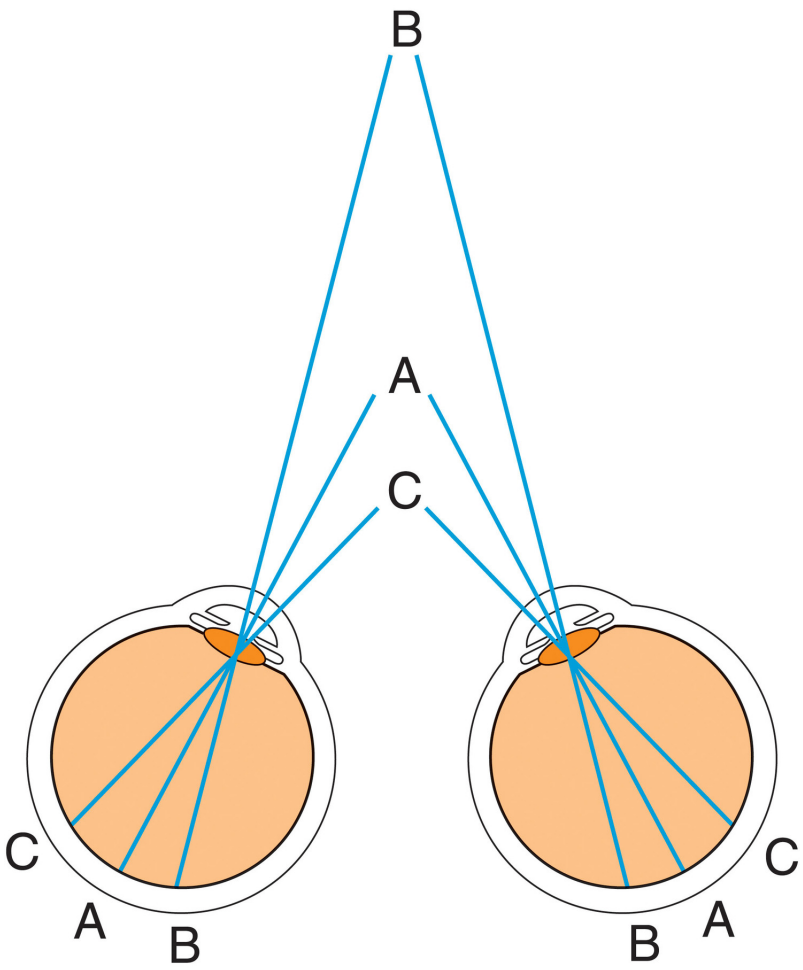
It seems like splitting the output of each eye between the two hemispheres would cause a major distortion of the image. However, if you look closely at Figure 10.5, you can see that the arrangement keeps related information together. Notice that the letter *A*, which appears in the person's left **visual field** (the part of the environment being registered on the retina), casts an image on the right half of *each* retina. The information from the right half of each eye will be transmitted to the right hemisphere. An image in the right visual field will similarly be projected to the left hemisphere. This is how researchers who study differences in the functions of the two cerebral hemispheres can project a visual stimulus to one hemisphere. They present the stimulus slightly to the left or to the right of the midline; the exposure time is too brief to allow the research participant to shift the eyes toward the stimulus, and with brief exposures, the information does not transfer to the other hemisphere.

? How does information about an object on your right end up in your left hemisphere?

Although it might appear in Figure 10.5 that information from both eyes is integrated in the lateral geniculate nuclei (LGN), information from each eye is kept separate and processed in discrete areas of the primary visual cortex (V1). If you close one eye of a research animal while the other is receiving visual stimulation, then stain V1 for cytochrome oxidase (which indicates metabolic activity), only the areas of V1 that were actively processing visual information will be darkly stained. When you look at the tissue under a microscope, you can see clear light and dark bands that appear like a fingerprint. These stripes are called ocular (left and right) dominance columns.

? How does retinal disparity help us see 3-D?

There is a good reason you have two forward-facing eyes, instead of one like the mythical Cyclops or one on each side of your head like many animals. The approximately 6-centimeter (cm) separation of your eyes produces **retinal disparity**, a discrepancy in the location of an object's image on the two retinas. Figure 10.6 shows how the image of distant objects in a scene falls toward the nasal side of each retina and closer objects cast their image in the temporal half. Retinal disparity is detected in the visual cortex, where different neurons fire depending on the amount of lateral displacement. Then this information is combined in the anterior parietal cortex with additional information about an object's shape and location to determine the distance of objects (J.-B. Durand et al., 2007). There are several good demonstrations of retinal disparity; the simplest is to hold your finger a foot (30 cm) in front of you and alternately close one eye and then the other while you notice how your finger moves relative to the background. The ViewMaster 3-D viewer you may have had as a child took advantage of your brain's retinal disparity detectors by presenting each eye with an image photographed at a slightly different angle. 3-D movies use the same principle, but differently polarized lenses in the special glasses separate the two images. A striking 3-D effect can also be obtained without a viewer from stereograms such as those created by Magic Eye.



Description

Figure 10.6 Retinal Disparity.
The image of an object to which the eyes are oriented (A) falls on the fovea, while the image of a more distant object (B) is displaced to the inside of each retina, and the image of a closer object (C) is displaced to the outside. This provides information to the brain for depth perception.

Source: Adapted from Schwartz, B. L. & Krantz, J. H. (2015).

As the rest of the story of vision unfolds, you will notice three themes that will help you understand how the visual system works: inhibition, modularity, and hierarchical processing. You will learn that neural *inhibition* is just as important as excitation, because it sharpens information beyond the processing capabilities of a system that depends on excitation alone. You will also learn that, like hearing and language, the visual system carries out its functions in discrete specialized structures, or *modules*, which pass information to each other in a serial, *hierarchical* fashion.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- In what ways is human vision adapted for our environment?

- How are the rod and cone systems specialized for different tasks? The two visual pathways?

COLOR VISION

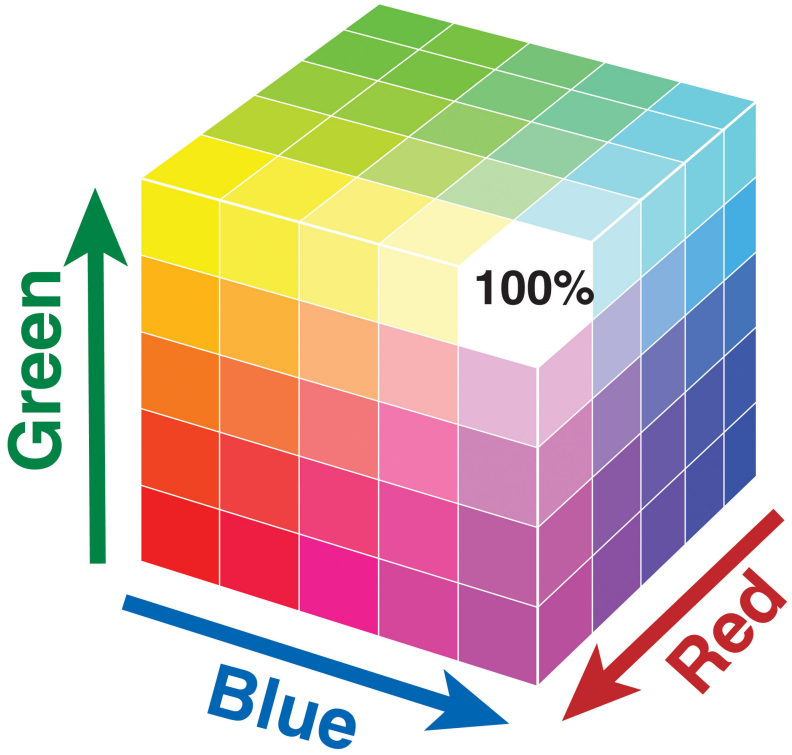
In Figure 10.1, you saw that there is a correspondence between color and wavelength; this would suggest that color is a property of the light reflected from an object and, therefore, of the object itself. However, wavelength does not always predict color, as Figure 10.7 illustrates. The circle on the left and the circle on the right appear to be different colors, although they reflect exactly the same wavelengths. Just as with the auditory terms *pitch* and *loudness*, the term *color* refers to the observer's experience rather than a characteristic of the object. Thus, it is technically incorrect to say that the light is red or that a book is blue, because *red* and *blue* are experiences that are imposed by the brain. However, in the interest of simplicity, we will be rather casual about this point in future discussions, as long as we understand that "red" and "blue" are experiences rather than object characteristics. To appreciate the experience of color, we must now examine the neural equipment that we use to produce that experience. Our understanding of color vision has been guided over the past two centuries by two competing theories: the trichromatic theory and the opponent process theory.

Figure 10.7 Independence of Wavelength and Color.
Although the circles are identical, they appear to differ in color due to the color contrast with their backgrounds.

Source: Copyright © 2013 Second Sight Medical Products, Inc.

Trichromatic Theory

After observing the effect of passing light through a prism, Sir Isaac Newton proposed in 1672 that white light is composed of seven fundamental colors that cannot themselves be resolved into other colors. If there are seven "pure" colors, this would suggest that there must be seven receptors and brain pathways for distinguishing color, just as there are five primary tastes (or six, if the fat receptor is confirmed). In 1852, Hermann von Helmholtz (whose place theory was discussed in Chapter 9) revived an idea of Thomas Young from a half century earlier. Because combining different amounts of just three colors of light can produce any color, Young and Helmholtz recognized that this must be due to the nature of the visual mechanism rather than the nature of light. They proposed a **trichromatic theory**—now known as the Young-Helmholtz theory—that just three color processes account for all the colors we are able to distinguish. They chose red, green, and blue as the primary colors because observers cannot resolve these colors into separate components as, for example, you can see red and blue in the color purple. When you watch television or look at an electronic device screen, you see an application of trichromatic color mixing: All the colors you see on the screen are made up of different intensities of tiny red, green, and blue dots (pixels) of light. This is illustrated in the color cube in Figure 10.8.



Description

Figure 10.8 Color Cube Demonstrating Trichromatic Theory.
All colors are possible by mixing different levels of green, blue, and red. Yellow is a result of high green and red levels with low blue levels, for example.

Opponent Process Theory

The trichromatic theory accounted for some of the observations about color perception very well, but it ran into trouble explaining why yellow also appears to observers to be a pure color. Ewald Hering (1878) "solved" this problem by adding yellow to the list of physiologically unique colors. But rather than assuming four color receptors, he asserted that there are only two—one for red *and* green and one for blue *and* yellow. **Opponent process theory** attempts to explain color vision in terms of opposing neural processes. In Hering's version, the photochemical in the red-green receptor is broken down by red light and regenerates in the presence of green light. The chemical in the second type of receptor is broken down in the presence of yellow light and regenerates in the presence of blue light.

? How do we distinguish colors?

Hering proposed this arrangement to explain the phenomenon of **complementary colors**, colors that cancel each other out to produce a neutral gray or white. (Note the spelling of this term; *complementary* means "completing.") In Figure 10.9, the visible spectrum appears as a circle rather than the horizontal continuum we saw in Figure 10.1. This rearrangement of the spectrum makes sense, because violet at one end of the spectrum blends naturally into red at the other end just as easily as the colors adjacent to each other on the spectrum blend into each other. Another reason the color circle makes sense is that any two colors opposite each other on the circle are complementary; mixing equal amounts of light from across the circle results in the sensation of a neutral gray tending toward white, depending on the brightness. An exception to this rule is the combination of red and green; they produce yellow, for reasons you will understand shortly.

Description

Figure 10.9 The Color Circle.
Colors opposite each other are complementary; that is, equal amounts of light in those colors cancel each other out, producing a neutral gray.

Another indication of complementarity is that overstimulation of the eye with one light makes the eye more sensitive to its complement. Stare at a red stimulus for a minute, and you will begin to see a green edge around it; then look at a white wall or a sheet of paper, and you will see a green version of the original object. This experience is called a **negative color aftereffect**; the butcher decorates the inside of the meat case with parsley or other greenery to make the beef look redder. Negative color after-effect is what one would expect if the wavelengths were affecting the same receptor in opposite directions, as Hering theorized. The flag in Figure 10.10 is a very good interactive demonstration of complementary colors and negative aftereffects.

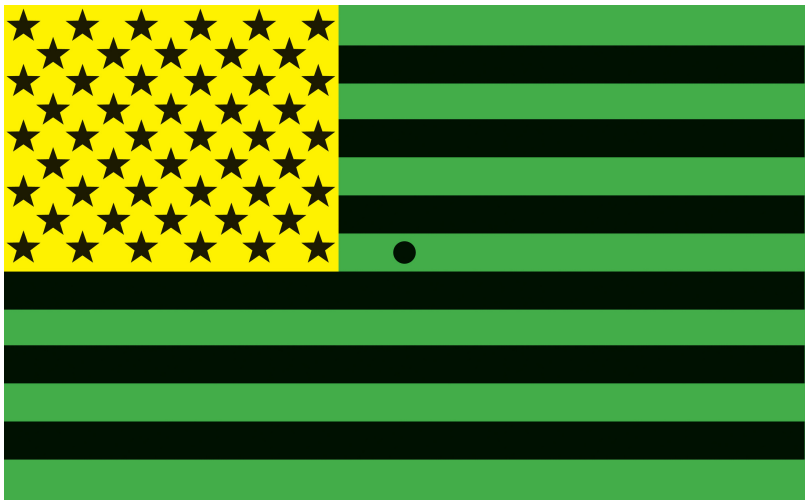
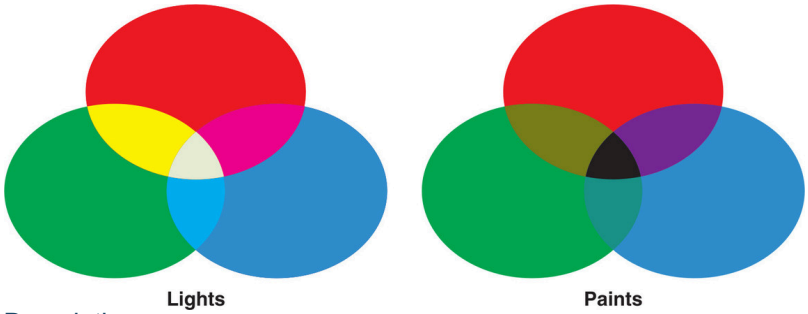


Figure 10.10 Complementary Colors and Negative Color Aftereffect.
Stare at the dot in the center of the flag for about a minute, and then look at a white surface (the ceiling or a sheet of paper); you should see a traditional red, white, and blue flag.

If this discussion of color mixing seems inconsistent with what you understood in the past, it is probably because you learned the principles of color mixing in an art class. The topic of discussion there was *pigment mixing*, whereas we are talking about *mixing light*. An object appears red to us because it reflects mostly long-wavelength (red) light, while it *absorbs* other wavelengths of light. The effect of light mixing is *additive*, whereas pigment mixing is *subtractive*. If we mix lights, we add wavelengths to the stimulus, but as we mix paints, more wavelengths are absorbed. For example, if you mix equal amounts of all wavelengths of light, the result will be white light; mixing paints in the same way produces black because each added pigment absorbs additional wavelengths of light until the result is total absorption and blackness (Figure 10.11).



Description

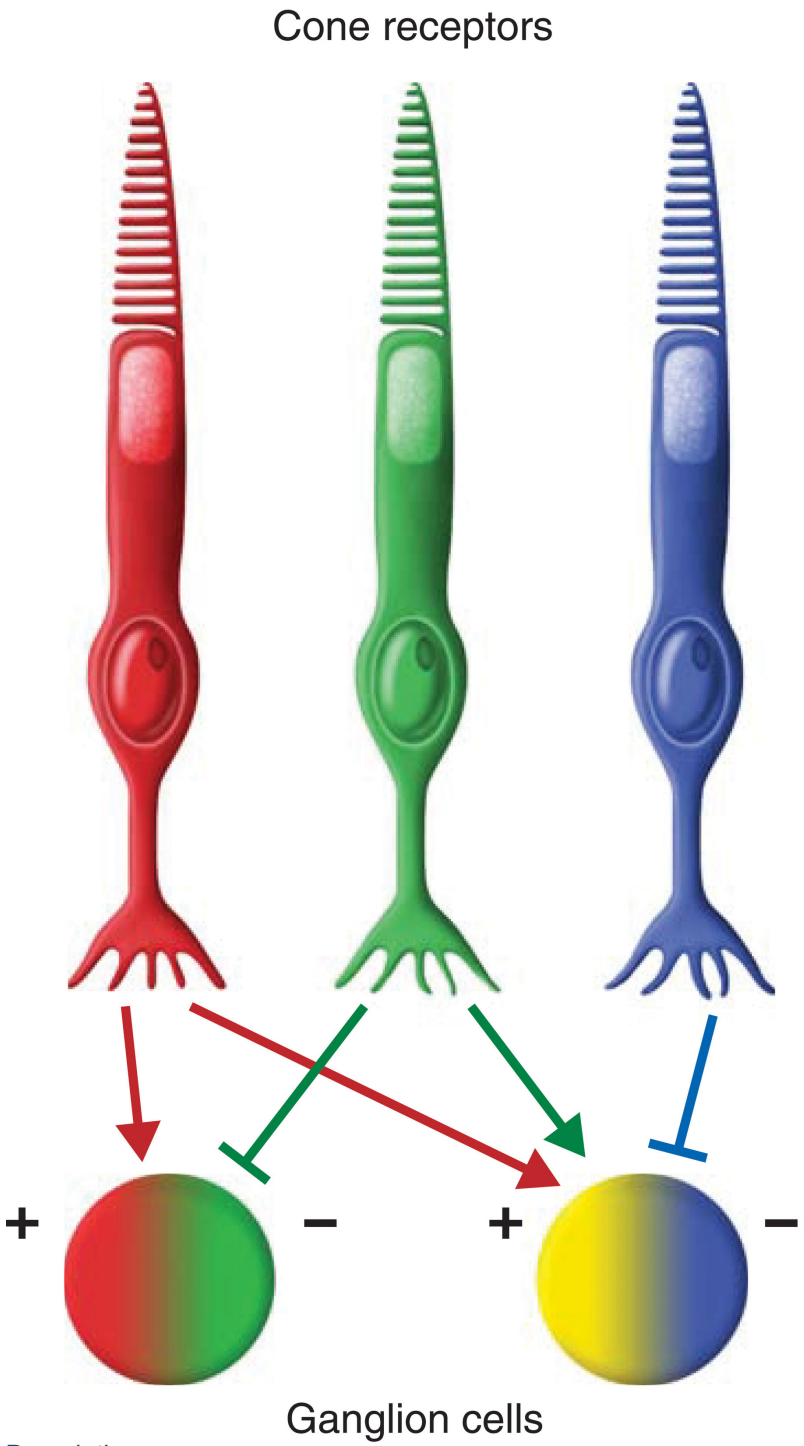
Figure 10.11 Mixing Lights Is Additive; Mixing Paints Is Subtractive.
The combination of all three primaries (or all colors) of light produces white; the same combination of pigments produces black, which is the lack of color.

Now, back to color vision theory. Although Hering's theory did a nice job of explaining complementary colors and the uniqueness of yellow, it received little acceptance. One reason was that researchers had trouble with Hering's assumption of a chemical that would break down in response to one light and regenerate in the presence of another. His theory was, in fact, in error on that point, but developments 100 years later would bring Hering's thinking back to the forefront.

A Combined Theory

The trichromatic and opponent process theories appear to be contradictory. Sometimes this means that one position is wrong and the other is right, but often it means that each of the competing theories is partly correct but just too simple to accommodate all the known facts. Hurvich and Jameson (1957) resolved the conflict with a compromise: They proposed that three types of color receptors—red sensitive, green sensitive, and blue sensitive—are interconnected in an opponent process fashion at the ganglion cells.

Figure 10.12 is a simplified version of how Hurvich and Jameson thought this combined color-processing strategy might work. Long-wavelength light excites "red" cones and the red-green ganglion cell to give the perception of red. Medium-wavelength light excites the "green" cones and inhibits the red-green ganglion cell, reducing its firing rate below its spontaneous level and signaling green to the brain. Likewise, short-wavelength light excites "blue" cones, which inhibits the yellow-blue ganglion cell, leading to a perception of blue. Light midway between the sensitivities of the "red" and "green" cones would stimulate both cone types. The firing rate in the red-green ganglion cell would not change, because equal stimulation and excitation from the two cones would cancel out; however, the cones' connections to the yellow-blue ganglion cell are both excitatory, so their combined excitation would excite the ganglion cell to produce a perception of yellow. If all three cones are stimulated at equal intensities, both ganglion cell types receive equal amounts of excitatory and inhibitory stimulation and, therefore, produce a perception of white (or a shade of gray, depending on the intensity of the light). According to this combined theory, there are three color processes at the receptors and four beyond the ganglion cells.



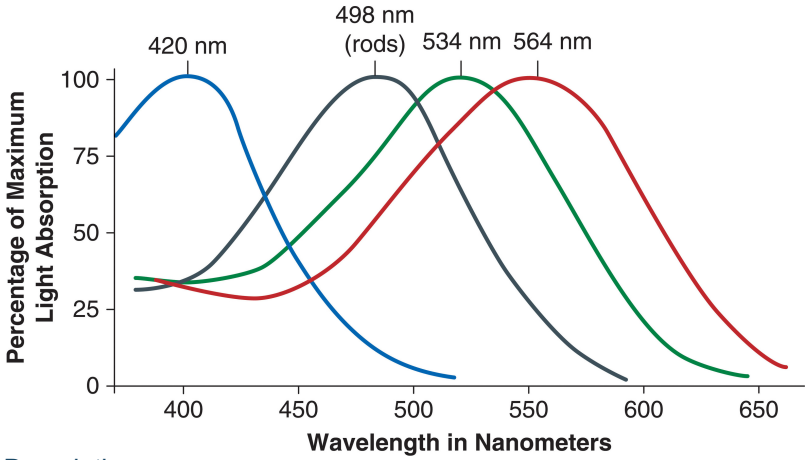
Description

Figure 10.12 Hurvich and Jameson's Proposed Interconnections of Cones Provide Four Color Responses and Complementary Colors.
According to their theory, excitation of "red" receptors activates red-green ganglion cells to produce the experience of red; excitation of "green" receptors inhibits the same ganglion cells, resulting in an experience of green. A sensation of yellow occurs when "red" and "green" receptors stimulate yellow-blue ganglion cells equally. Inhibition of those ganglion cells by "blue" receptors produces a sensation of blue.

Source: Adapted from Schwartz, B. L. & Krantz, J. H. (2015).

This scheme does explain very nicely why yellow would appear pure just like red, green, and blue do. Also, it is easy to understand why certain pairs of colors are complementary instead of producing a blended color. For example, you could have a color that is reddish blue (purple) or greenish yellow (chartreuse) but not a reddish green or a bluish yellow. You can try this out in any computer drawing program: Make a gradient that is red on one side and green on the other, and you'll see that where they meet is gray. Negative aftereffects can be explained as overstimulation "fatiguing" a ganglion cell's response in one direction, causing a rebound in the opposite direction and a subtle experience of the opposing color. By the way, this is our first example of the significance of all that interconnectedness in the retina that we saw back in Figure 10.4.

Evidence for this combined trichromatic/opponent process theory would be almost a decade away, however, because it depended on the development of more precise measurement capabilities. Support came in two forms. First, researchers produced direct evidence for three color receptors in the retina (K. Brown & Wald, 1964; Dartnall, Bowmaker, & Mollon, 1983; W. B. Marks, Dobelle, & MacNichol, 1964). The researchers shone light of selected wavelengths through individual receptors in eyes that had been removed from humans for medical reasons or shortly after their death; they measured the light that passed through to determine which wavelengths had been lost through absorption. The absorbed wavelengths indicated the ones the receptor's photochemical was sensitive to. Figure 10.13 shows the results from a study of this type. Note that there are three distinct color response curves (plus a response curve for rods), just as Hurvich and Jameson predicted. We should point out that the "red" cone's sensitivity is actually closer to orange, but tradition is tradition, so we continue to refer to its preferred color as red.



Description

Figure 10.13 Relative Absorption of Light of Various Wavelengths by Visual Receptors.
Note that each type of cone responds best to wavelengths corresponding to blue, green, and red light, though each responds to other wavelengths as well.

Source: Adapted from "Visual Pigments of Rods and Cones in Human Retina," by Bowmaker and Dartnall, 1980, *Journal of Physiology, 298,* pp. 501–511. Copyright 1980, with permission from John Wiley & Sons, Inc.

Let's look at two additional features of these results. Like the tuning curves for frequency we saw in Chapter 9, these curves are not very sharp; each receptor has a sensitivity peak, but its response range is broad and overlaps with that of its neighbors. This means that the medium-wavelength cones could be active because the stimulus is "green" light or because they are being stimulated with intense "blue" light. The system must *compare activity in all three types of cones* to determine which wavelengths you are seeing. This "comparison" does not occur at the level of

awareness; it is an automatic neural process, like the one that sharpens frequency discrimination and the activity of coincidence detectors in sound localization.

The second feature is related to the evolution of color vision. Notice that in Figure 10.13 the medium- and long-wavelength curves (green and red, respectively) are distant from the short-wavelength curve (blue) but are very close to each other. Genetic research indicates that the genes for the photopigments in the medium- and long-wavelength cones evolved from a common precursor gene relatively recently (*only* about 35 million years ago), but the genes for the short-wavelength cones and for the rod receptors split off from their precursor much earlier. Indeed, the “red” and “green” genes are adjacent to each other on the X chromosome, and they are 98% identical in DNA (Gegenfurtner & Kiper, 2003). Because the genes are on the X chromosome, red-green color blindness is a sex-linked trait and tends to affect males many times more than females. (See the discussion of X-linked traits in Chapter 1.)

Recently, researchers were able for the first time to study individual cones in the eyes of human volunteers. Surprisingly, stimulation of two thirds of the cones identified as red sensitive or green sensitive yielded a response of “white” much more often than the expected “red” or “green” (Figure 10.14; Sabesan, Schmidt, Tuten, & Roorda, 2016). This makes sense, because very few cones are needed to determine an object’s color, but numerous cells are required for discriminating fine details. This emphasis on light detection in the majority of cones may be useful for some proposed treatments for retinal blindness (see A Further Look on restoring vision), in that improving cone function will increase overall light perception. You may wonder how the researchers were able to make repeated measurements of photocells, given that the eye is constantly moving. Ingeniously, they used the same technology that enables a telescope to track a star.

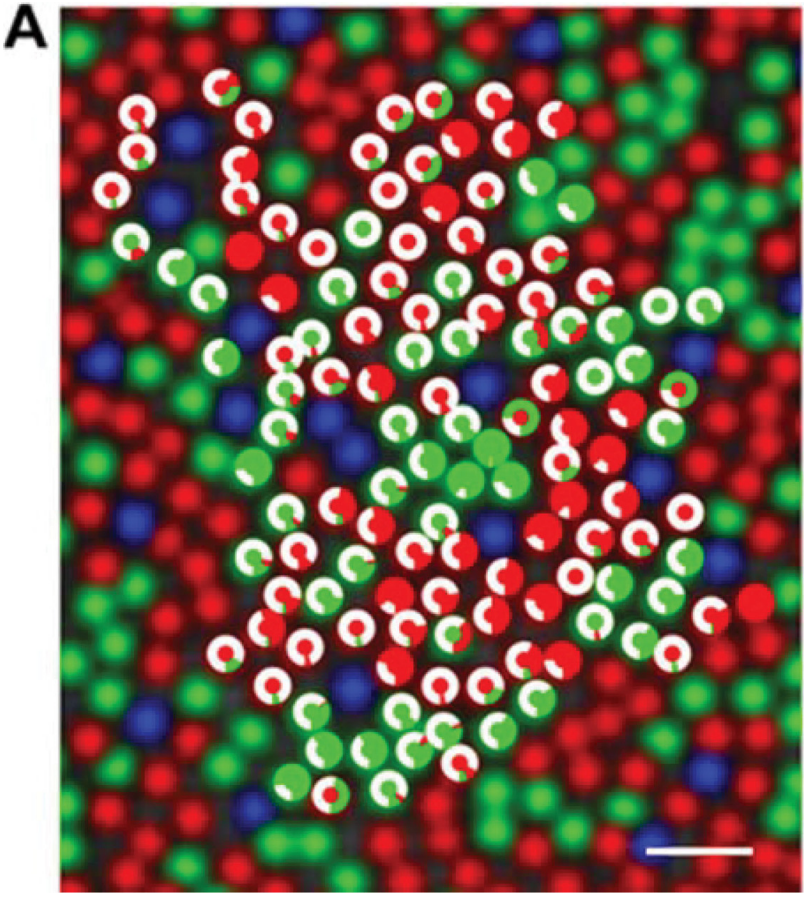


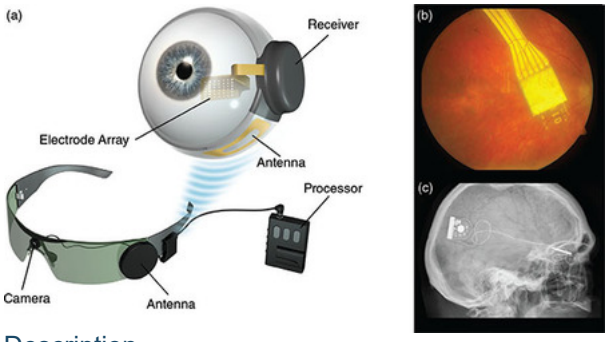
Figure 10.14 Cones Respond to More Than Specific Colors.
The inner circles denote the cones' color preferences, either red or green. (Blue-sensitive cones were not tested but are indicated by solid blue dots.) The proportion of red or green in the outer circle indicates how much the cone is specialized for that color, *versus* its ability to detect all wavelengths (indicated in white).

Source: Figure 1a from Sabesan, R., Schmidt, B. P., Tuten, W. S., & Roorda, A. (2016). The elementary representation of spatial and color vision in the human retina. *Science Advances*, 2, e1600797-e1600797.

Reprinted with permission of AAAS from Sabesan, R., Schmidt, B. P., Tuten, W. S., & Roorda, A. (2016). The elementary representation of spatial and color vision in the human retina. Science Advances, 2, e1600797-e1600797. © The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC) http://creativecommons.org/licenses/by-nc/4.0/

A Further Look:

Restoring Lost Vision



Description

(a) Copyright © 2013 Second Sight Medical Products, Inc.
(b) and (c) Figure 2a and b of Stingl K, Bartz-Schmidt KU, Besch D, et al. Subretinal Visual Implant Alpha IMS--Clinical trial interim report. Vision Res. 2015;111(Pt B):149-160. Copyright © 2015 The Authors. Published by Elsevier Ltd. Licensed under CC BY 4.0, https://creativecommons.org/licenses/by/4.0/

The World Health Organization (2019) reports that at least 2.2 billion people have a vision impairment or blindness; fortunately, researchers now have a variety of promising strategies for restoring lost vision. When the photoreceptors have lost function due to retinitis pigmentosa or macular degeneration, they can be bypassed by electrodes inserted into the retina. The Argus II, for example, uses a video camera and a processor to send a pattern of activation wirelessly to an array of 60 electrodes, which stimulate the ganglion cells (a in the figure; Markowitz et al., 2018). The Alpha AMS replaces the camera with 1,600 light-sensing photodiodes inserted among the bipolar cells (Edwards et al., 2018). The processor communicates between the photodiodes and the electrodes (b and c in the figure) via a coil mounted on the scalp behind the ear. Eliminating the external camera allows the user to look around by moving the eyes rather than turning the head. The minimal resolution of these two methods enables basic capabilities such as distinguishing people from background and identifying food on a plate.

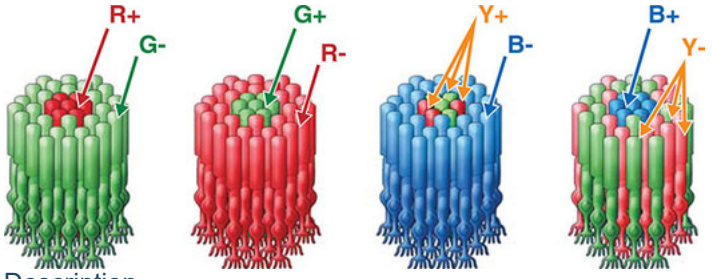
Of course, the ideal would be to make the damaged retina respond to light on its own, and research teams are making progress toward accomplishing this. Optogenetic methods have been used with some success in rodents to insert light-sensitive channels or light-sensitive substances into bipolar cells and ganglion cells, so those cells are able to respond to light (Baker & Flannery, 2018). Another alternative is the use of stem cells. Inserting retinal pigment epithelium (a layer that supports and nourishes the retina) grown from stem cells rescued degenerating photoreceptors

and improved vision in four of five patients; in another study, it enabled reading at 60 to 80 words per minute in two individuals who had been unable to read at all before (da Cruz et al., 2018; Kashani et al., 2018). Introducing the *RPE65* gene into the retinas of individuals deficient in an enzyme required for receptor functioning and survival substantially improved vision in 65% of the participants; the procedure won the first FDA approval for gene therapy for an inherited retinal disease (Russell et al., 2017). But gene therapy requires finding the right gene and discovering the best carrier for introducing the gene. Three attempts to treat age-related macular degeneration have been unsuccessful, but additional trials are in progress (Ho & Avery, 2019).

Trichromatic vision is certainly beneficial in appreciating art, but we might well ask what evolutionary benefits compelled its development. An obvious advantage was an enhanced ability to distinguish ripe red fruit among green foliage and to distinguish young, tender leaves from darker ones. In addition, comparisons of primate genomes indicate intriguing parallels between the appearance of genes for trichromacy, the decreases in olfactory and pheromone receptor genes, and the development of visual sexual signals such as the reddened and swollen sexual skin in female baboons and Old World monkeys (Gilad, Wiebe, Przeworski, Lancet, & Pääbo, 2004; J. Zhang & Webb, 2003). The importance of the red-green end of the spectrum is suggested by the fact that only 10% of human cones have their sensitivity in the blue end of the spectrum (see Figure 10.14). Analyzing 5,000 photographs from the savannas of Botswana, researchers concluded that this balance matches the distribution of colors in the environment in which humans are believed to have evolved (Garrigan et al., 2010).

Additional confirmation of the trichromatic/opponent process theory came when researchers found the predicted color-opponent cells in monkeys, both in the retina and in the lateral geniculate nucleus of the thalamus (De Valois, 1960; De Valois, Abramov, & Jacobs, 1966; Gouras, 1968). Figure 10.12 shows two types of opponent cells, one that is excited by red and inhibited by green (R+G−) and one that is excited by yellow and inhibited by blue (Y+B−); Russell De Valois and his colleagues (1966) identified two additional types that were the inverse of the previous two: green excitatory/red inhibitory (G+R−) and blue excitatory/yellow inhibitory (B+Y−).

A surprise was that some of the color-opponent ganglion cells receive their input from cones that are arranged in two concentric circles (Gouras, 1968; Wiesel & Hubel, 1966). The cones in the center and those in the periphery have color-complementary sensitivities (see Figure 10.15). Why all this complexity? First, the opposition of cones at the ganglion cells provides wavelength discrimination that individual cones are incapable of producing (E. B. Goldstein, 1999)—an example of the “neural comparison” we referred to earlier. The concentric-circle receptor fields also enhance information about color contrast between adjacent areas. This mode of information sharpening will become clearer when we look at how the retina distinguishes the edge of an object.



Description

Figure 10.15 Receptive Fields of Center-Surround Color-Opponent Ganglion Cells. The cones in the center and the cones in the periphery respond to colors that are complementary to each other. (Note that the yellow signal is due to the combined outputs of red and green cones.) The center cones excite the ganglion cell, and the cones in the periphery inhibit it.

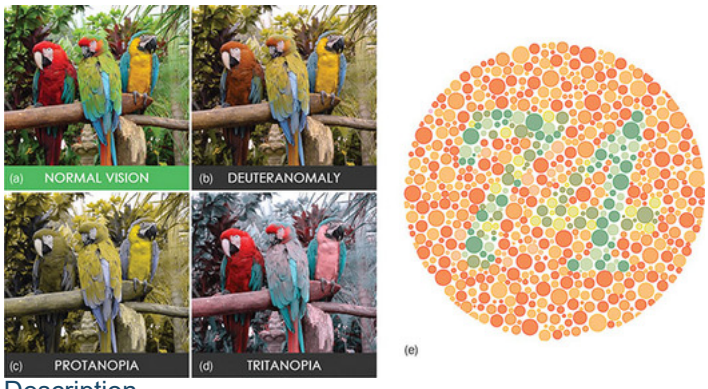
Source: Carolina Hrejsa/Body Scientific Intl. Based on the findings of De Valois et al. (1966).

A theory is considered successful if it is consistent with the known facts, can explain those facts, and can predict new findings. The combined trichromatic and opponent process color theory meets all three criteria: (1) It is consistent with the observation that all colors can be produced by using red, green, and blue light. (2) It can explain why observers regard red, green, blue, *and* yellow as pure colors. It also explains complementary colors, negative aftereffects, and the impossibility of color experiences such as greenish red. (3) It predicted the discovery of three photopigments and of the excitatory/inhibitory neural connections at the ganglion cells.

Color Blindness

Color blindness (or the more accurate term, color vision deficiency) occurs when an individual has a poor or absent response from one or more cone types, leading to difficulty distinguishing certain colors. It is an intriguing curiosity, but more than that, it has played an important role in our understanding of color perception by scuttling inadequate theories and providing the inspiration for new ones. There are very few completely color-blind people—about 1 in every 100,000. They usually have an inherited lack of cones; limited to rod vision, they see in shades of gray, they are very light sensitive, and they have poor visual acuity. More typically, a person is partly color-blind, due to a defect in one of the cone systems rather than a total lack of cones.

There are two major types of retinal color deficiency. A person who is red-green color-blind sees these two colors but is unable to distinguish between them (this is either protanopia with absence of red receptors, or deuteranopia with absence of green receptors). We know something about what color-blind people experience by noting which colors color-blind people confuse and from studying a few rare individuals who are color-blind in only one eye. When a red-green color-blind colleague of one of the authors was describing his experience of color, he explained that green grass appeared to be the same color as peanut butter! We're not sure what peanut butter actually looked like to him, but he did say that he found grass and trees "very beautiful." People in the much rarer second color-blind group, tritanopia, have difficulty distinguishing blue, so their world appears in variations of red and green. Many partly color-blind individuals are unaware that they see the world differently from the rest of us. Figure 10.16 (a–d) shows a scene as it is perceived by people with normal color vision and by those with color vision deficiencies. Color blindness can be detected by having the individual match or sort colored objects or with a test like the one illustrated in Figure 10.16e.



Description

Figure 10.16 What a Person With Color Deficiency Sees.
A scene as viewed by an individual with normal color vision (a) and with deuteranopia (b), protanopia (c), and tritanopia (d). Most people see the number 74 in this plate from the Ishihara test for color blindness, but a person with color deficiency sees the number 21; a totally color-blind person may not see a number.

What is it like to be color-blind?

People with red-green color blindness show a deficiency in either the red end of the spectrum or in the green portion; this suggests that the person lacks either the appropriate cone or the photochemical. Acuity is normal in both groups, so there cannot be a lack of cones. Some individuals are unusually sensitive to green light, and the rest are sensitive to red light; this suggests that in one case the normally red-sensitive cones are filled with green-sensitive photochemical and in the other the normally green-sensitive cones are filled with red-sensitive chemical. The condition is due to a mutation on the X chromosome, so it is considerably more prevalent in males (5.0% to 8.0%, versus 0.5% to 1.0%). Tritanopia is usually due to an inherited lack of blue-receptive cones, but it can be caused by blunt trauma to the eye. Unlike red-green color blindness, the deficiency is not X-linked, so it occurs with equal frequency in males and females (about 1.0%).

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- Summarize the three color vision theories described here.
- What is the benefit of the color-opposed concentric circle receptor fields?
- What causes color blindness?

FORM VISION

Just as the auditory cortex is organized as a map of the cochlea, the visual cortex contains a map of the retina. Russell De Valois and his colleagues demonstrated this point when they presented the image in Figure 10.17a to monkeys that had been injected with radioactive 2-deoxyglucose. The animals were sacrificed and their brains placed on photographic film. Because the more active neurons absorbed more radioactive glucose, they exposed the film more darkly in the autoradiograph in Figure 10.17b; this produced an image of the stimulus that appears to be wrapped around the monkey's occipital lobe (Tootell, Silverman, Switkes, & De Valois, 1982).

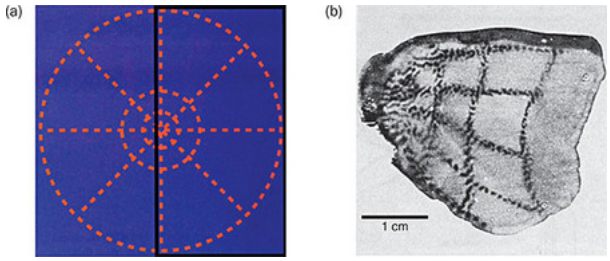


Figure 10.17 Deoxyglucose Autoradiograph Showing Retinotopic Mapping in Visual Cortex.
Monkeys were given radioactive 2-deoxyglucose and then shown the design in (a). They were sacrificed, and a section of their visual cortical tissue was placed on photographic film. The exposed film showed a pattern of activation (b) that matched the design.

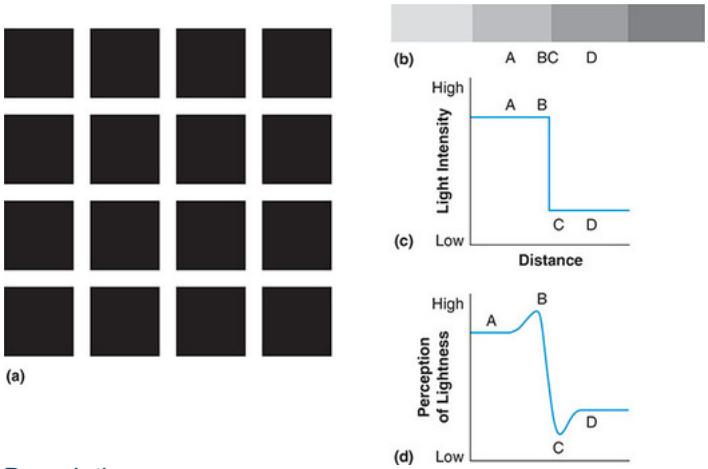
Source: From "Deoxyglucose Analysis of Retinotopic Organization in Primate Striate Cortex," by R. B. H. Tootell et al.," *Science*, 218, pp. 902–904. Reprinted with permission from AAAS.

This result tells us that just as there is a tonotopic map of the basilar membrane in the auditory cortex, we have a **retinotopic map** in the visual cortex, meaning that adjacent retinal receptors activate adjacent cells in the visual cortex. However, this

does not tell us how we see images; transmitting an object's image to the cortex like a television picture does not amount to perception of the object. Object perception is a two-stage affair. In this section we will discuss **form vision**, the detection of an object's boundaries and features (such as texture). We will discuss the second component, object recognition, a bit later. The story that unfolds here is about more than perception; it provides a model for understanding how the brain processes information in general. It is also a story that begins not in the cortex but in the retina itself.

Contrast Enhancement and Edge Detection

Detecting an object's boundaries is the first step in form vision. The nervous system often exaggerates especially important sensory information (as we saw in binaural sound localization in Chapter 9). In the case of boundaries, the retina uses **lateral inhibition**, where each neuron's activity inhibits the activity of its neighbors and in turn they inhibit its activity, to enhance the contrast in brightness that defines an object's edge. To demonstrate this enhancement for yourself, look at the Hermann grid illusion in Figure 10.18a and the Mach band illusion in Figure 10.18b. The Hermann grid is the more dramatic of the two illusions, but the simplicity of the Mach band graphic makes it easier to explain, so we will focus on it. Each bar in the Mach band image is consistent in brightness across its width, but it looks a bit darker on the left and a bit lighter on the right than it does in the middle. (If you don't see a difference at the edges, you may notice that the bars seem slightly curved. This is because the illusion suggests subtle shadowing on the left side of each bar.) An illusion is not simply an error of perception but an exaggeration of a normal perceptual process, which makes illusions very useful in studying perception. See A Further Look for more on visual illusions.



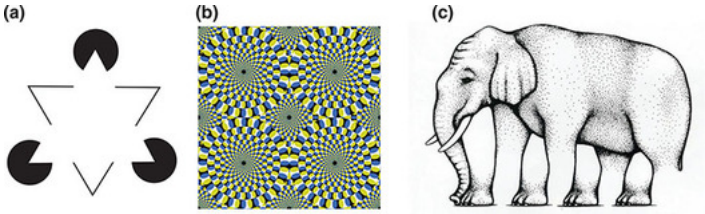
Description

Figure 10.18 Demonstration of Lateral Inhibition.
(a) In the Hermann grid illusion, lateral inhibition causes you to see small, grayish blotches at the intersections of the large squares. (b) The Mach band illusion is another example. Each band is consistent in brightness across its width, as shown in the graph of light intensity in (c). But where the bands meet, you experience a slight enhancement in brightness at the edge of the lighter band and a decrease in brightness at the edge of the darker band (e.g., at points B and C). This effect is represented graphically in (d). Exaggeration of brightness contrast at edges helps us see the boundaries of objects.

Sources: (a) Based on Hermann (1870). (b) From *Mach Bands: Quantitative Studies on Neural Networks in the Retina* (fig. 3.25, p. 107), by F. Ratcliff, 1965. San Francisco: Holden-Day. Copyright © Holden-Day Inc.

A Further Look:

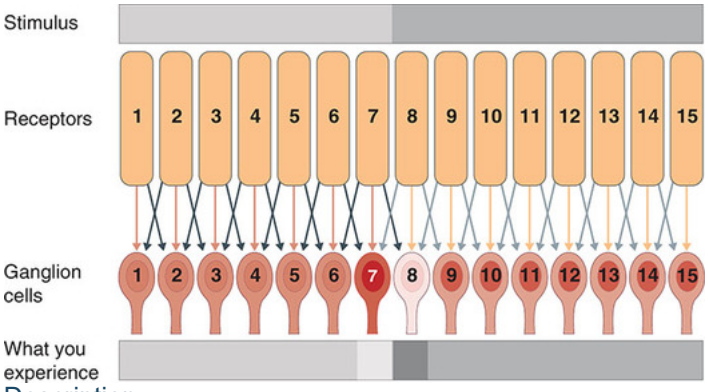
Neural Bases of Visual Illusions



Description

As you have been learning in this chapter, visual signals are processed at multiple levels; the Mach band illusion, for example, occurs at the retinal level, whereas other features of the visual world are not processed until the cortex. Illusions are more than entertaining novelties; they also can tell us how the visual mechanism converts retinal stimulation into a meaningful visual experience. This includes how we distinguish the edges or boundaries of objects, separate objects from each other, and make sense of the contents of an image. Look at the Kanizsa triangle (a) for instance. The white triangle you see is an illusion, created when the cortical area V2 “fills in” the triangle’s boundaries that are suggested by the missing portions of the circles and the actual triangle (von der Heydt, Peterhans, & Baumgartner, 1984). The middle image (b), called the Fraser-Wilcox or peripheral drift illusion, fools your brain into thinking the circles are rotating even though you obviously are looking at a printed page. This happens in the medial temporal lobe (MT), which is responsible for extracting motion information. The yellow and blue are processed by the same ganglion cells, and the MT interprets the rapid alternations between the two colors as motion. Finally, the cortex is responsible for combining features from the two processing streams into a singular experience. In the last image in the figure (c), how many legs does the elephant have? Is there anything odd about them? It may take a bit of study to see why the elephant is clearly an impossible animal—understanding what you’re seeing here requires the contribution of your frontal lobes (Shepard, 1990).

Figure 10.19 will help you understand how your retinas produce the illusion using lateral inhibition. In this case, the inhibition is delivered by horizontal cells to nearby bipolar cells. The critical point in the illustration is at ganglion cells 7 and 8. Ganglion cell 7 is inhibited less than ganglion cells 1 to 6; this is because the receptors to its right are receiving very little stimulation and producing low levels of inhibition. This lesser inhibition of ganglion cell 7 creates a sensation of a lighter band to the left of the border, as indicated at the bottom of the illustration. Similarly, ganglion cell 8 is inhibited more than its neighbors to the right, because the receptors to its left are receiving greater stimulation and producing more inhibition. As a result, the bar appears darker to the right of the border. This lateral inhibition is strikingly similar to what we saw in the previous chapter, which sharpens frequency information.

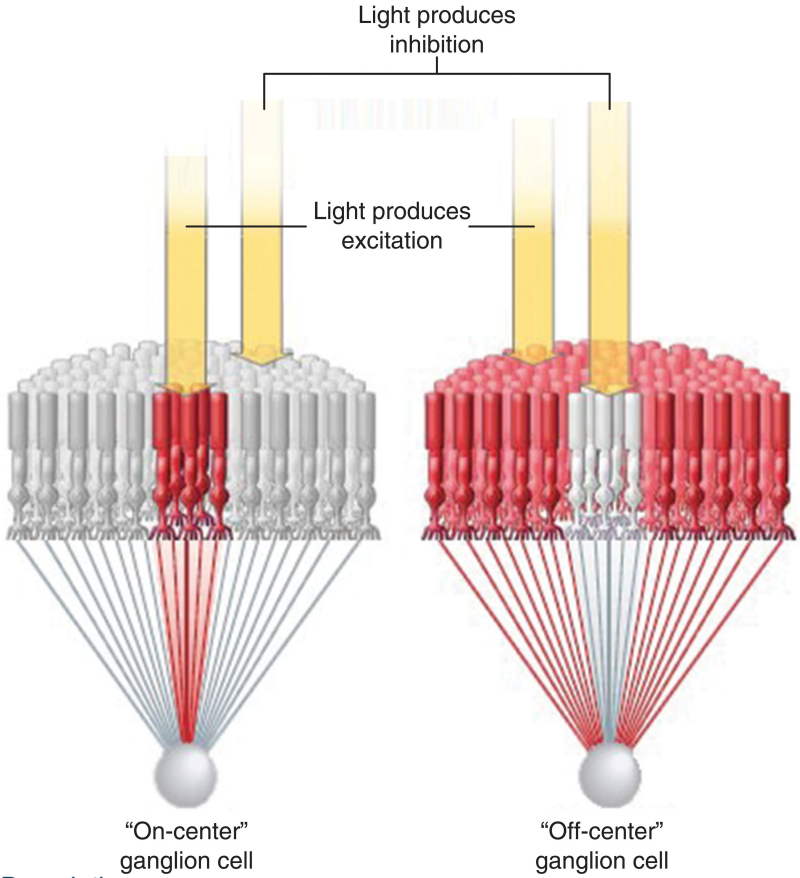


Description

Figure 10.19 The Neural Basis of the Mach Band Illusion.
The bar at the top represents the middle two bands from Figure 10.18b. Red arrows indicate excitation, and gray arrows indicate inhibition. All ganglion cells are activated, but ganglion cell 7 is activated most; like 1 through 6, it receives more stimulation from the brighter stimulus, but it receives less inhibition from the receptors to the right. Likewise, ganglion cell 8 receives minimal stimulation, plus it receives more inhibition from the receptors to the left than do cells 9 through 15. As a result, the light bar appears lighter at its border with the dark bar, which in turn appears darker at its border. (Cells between the receptors and ganglion cells have been omitted for simplicity. Also, you would see some gradation of contrasts, because the inhibitory connections extend farther than the adjacent cell.)

Carolina Hrejsa/Body Scientific Intl.

Actually, this description is more appropriate for the eye of the horseshoe crab, where lateral inhibition was originally confirmed by electrical recording; in fact, Figure 10.18d is a graph of data from the horseshoe crab's eye (F. Ratliff & Hartline, 1959). The principle is the same in the mammalian eye, but each ganglion cell's receptive field is made up of several receptors arranged in circles, like the color-coded circular fields we saw earlier (Kuffler, 1953). Light in the center of the field has the opposite effect on the ganglion cell from light in the surround. In *on-center* cells, light in the center increases firing, and light in the *off surround* reduces firing below the resting levels. Other ganglion cells have an *off center* and an *on surround*. Figure 10.20 illustrates these two types of ganglion cells.

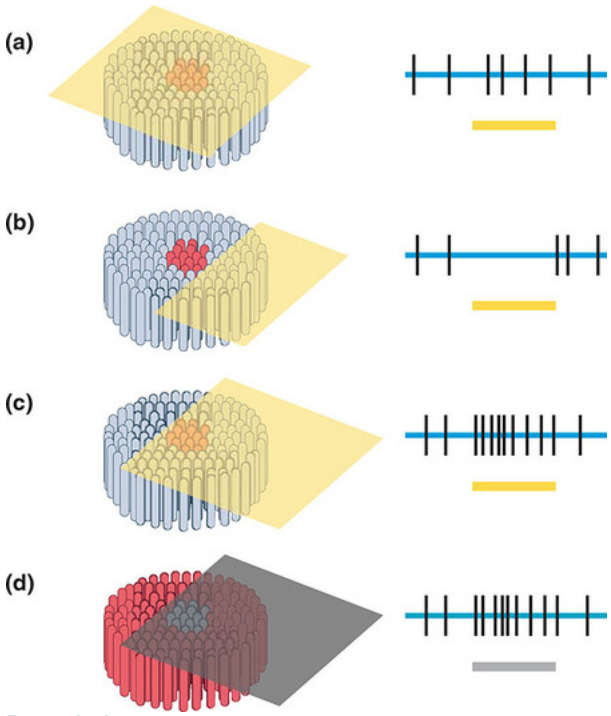


Description

Figure 10.20 Effect of Light on Center and Surround of Receptive Field.
The receptive fields and ganglion cells are shown in cross section. The connecting cells between the receptors and the ganglion cells have been omitted for simplicity.

Carolina Hrejsa/Body Scientific Intl.

These ganglion cells are good at detecting spots of light or darkness, but their contribution to vision is as light–dark contrast detectors (Hubel, 1982). Look at the illustrations in Figure 10.21. Light falling across the entire field will have little or no effect on the ganglion cell's firing rate, because the excitation and inhibition cancel each other out (Figure 10.21a). Light that falls only on the off surround will suppress firing in the ganglion cell (Figure 10.21b). But the ganglion cell's firing will be at its maximum when the stimulus falls on all of the on center and only a part of the off surround, as in Figure 10.21c. Figure 10.21d represents what happens in an off-center ganglion cell when its receptors are stimulated by an object that is darker than the background (or by a shadow). Because the dark image falls across the entire "off" center but only part of the "on" surround, the cell's activity is high. We are so accustomed to thinking of vision in terms of light stimulation that we neglect the importance of dark stimulation. The fact is that off-center ganglion cells outnumber on-center cells two to one in the human retina, and for good reason. When researchers analyzed photos taken in several settings ranging from the streets of Philadelphia to the plains of Africa, they found that dark-on-light contrasts were 10% to 20% more numerous than light contrasts (C. P. Ratliff, Borghuis, Kao, Sterling, & Balasubramanian, 2010). When they created a mathematical model of the ideal system for processing these scenes, it predicted the smaller and more numerous off-center cells found in the retina. We will see the significance of this light–dark contrast mechanism in the next section.



Description

Figure 10.21 Effects of a Border on an On-Center and an Off-Center Ganglion Cell. The receptors shown in (a)–(c) are connected to an on-center ganglion cell, and those in (d) are connected to an off-center cell. The vertical marks on the blue bars indicate neural responses; the yellow line underneath indicates when the light was on, and the dark line indicates presence of the dark image. Notice that the greatest activity occurs in the ganglion cell when the (appropriate) stimulus falls on all of the center but less than the entire surround.

Carolina Hrejsa/Body Scientific Intl.

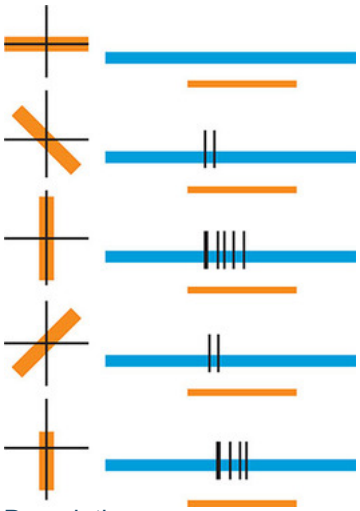
Hubel and Wiesel's Theory

Cells in the lateral geniculate nucleus (LGN) have circular receptive fields just like the ganglion cells from which they receive their input. The receptive fields of visual neurons in the cortex, however, turn out to be surprisingly different. David Hubel and Torsten Wiesel (1959) were probing the visual cortex of anesthetized cats as they projected visual stimuli on a screen in front of the cats. Their electrode was connected to an auditory amplifier so that they could listen for indications of active cells. They were manipulating a glass slide with a black dot on it in the projector—a very effective stimulus with ganglion cells and LGN cells—and getting only vague and inconsistent responses,

> when suddenly over the audio monitor the cell went off like a machine gun. After some fussing and fiddling we found out what was happening. The response had nothing to do with the black dot. As the glass slide was inserted, its edge was casting onto the retina a faint but sharp shadow, a straight dark line on a light background. (Hubel, 1982, p. 517)

? How do we detect objects' boundaries?

Hubel and Wiesel then began exploring the receptive fields of these cortical cells by projecting bars of light on the screen. They found that an actively responding cell would decrease its responding when the stimulus was moved to another location or rotated to a slightly different angle. Figure 10.22 shows the changes in response in one cell as the orientation of the stimulus was varied. Hubel and Wiesel called these cortical cells simple cells. A **simple cell** responds to a line or an edge that is at a specific orientation and at a specific place on the retina.

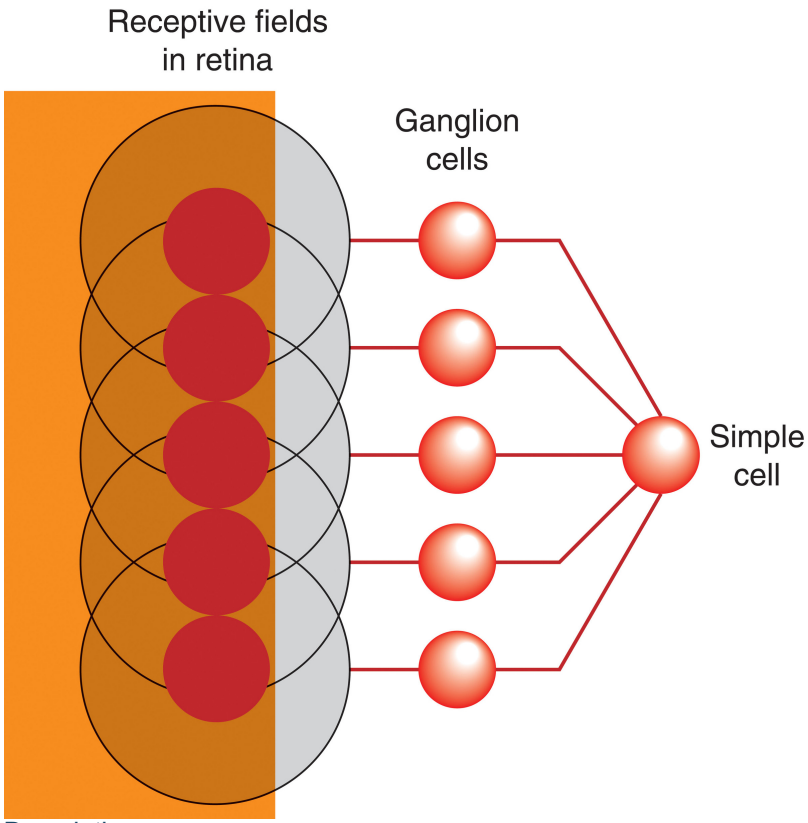


Description

Figure 10.22 Responses to Lines at Different Orientations in a Simple Cell Specialized for Vertical Lines.
The vertical hatch marks represent neural responses, and the orange line underneath indicates when the stimulus occurred. Notice that the response was greatest when the line was closest to the cell's "preferred" orientation (vertical) and least when the orientation was most discrepant. In the last example, the response was diminished because the stimulus failed to cover the cell's entire field (indicated by the stimulus being off-center of the crosshair).

Source: Adapted from "Receptive Fields of Single Neurons in the Cat's Striate Cortex," by D. H. Hubel and T. N. Wiesel, 1959, Journal of Physiology, 148, pp. 574–591, Fig. 3. © 1959 by The Physiology Society.

How can we explain the surprising shift in specialization between ganglion cells and cortical cells? To understand this, imagine several contrast-detecting circular fields arranged in a straight line, like those in Figure 10.23. (Notice that the fields overlap each other; by now you shouldn't be surprised that receptors would share their output with multiple ganglion cells.) Then, connect the outputs of their ganglion cells to a single cell in the cortex—one of Hubel and Wiesel's simple cells. You now have a mechanism for detecting not just spots of light–dark contrast but a contrasting edge, such as in the border of an object that is lighter or darker than its background. Fields with "on" centers would detect a light edge, like the one in the figure, and a series of circular fields with "off" centers would detect a dark edge.



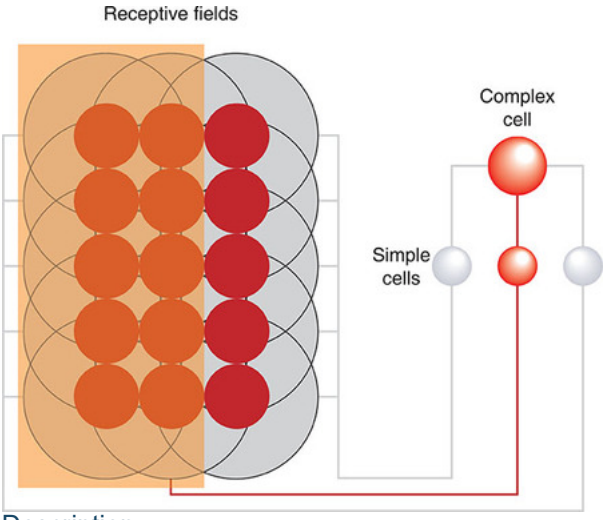
Description

Figure 10.23 Hubel and Wiesel's Explanation for Responses of Simple Cells. When the edge is in this position, the ganglion cell for each of the circular fields increases its firing. (The fields shown here have on centers.) The ganglion cells are connected to the same simple cell, which also increases firing, indicating that an edge has been detected. This particular arrangement would be specialized for a vertical light edge.

In other layers of the cortex, Hubel and Wiesel found complex cells. A **complex cell** continues to respond when a line or an edge moves to a different location, as long as it is not too far from the original site. They explained the complex cell's ability to continue responding in essentially the same way they explained the sensitivity of simple cells. They assumed that complex cells receive input from several simple cells that have the same orientation sensitivity but whose fields are adjacent to each other on the retina. This arrangement is illustrated in Figure 10.24. Notice that as the edge moves horizontally, different simple cells will take over, but the same complex cell will continue responding. However, if the edge rotates to a different orientation, this

complex cell will stop responding, and another complex cell specific for that orientation will take over. Connecting several simple cells to a single complex cell enables the complex cell not only to keep track of an edge as it moves but also to *detect* movement.

Figures Brought to Life



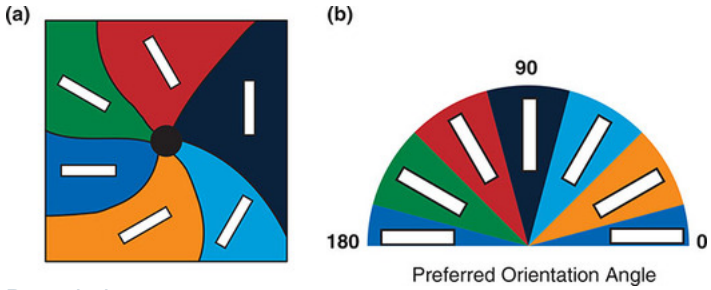
Description

Figure 10.24 Hubel and Wiesel's Explanation for Responses of Complex Cells. A complex cell receives input from several simple cells, each of which serves a group of circular fields (as in Figure 10.23). As a result, the complex cell continues to respond as the illuminated edge moves to the left or to the right. (Ganglion cells have been eliminated for simplicity.)

The feasibility of this kind of arrangement has received support from an interesting source—artificial neural networks. Lau, Stanley, and Dan (2002) trained a network so that its output "neurons" gave the same responses to bar-shaped stimuli as those recorded from complex cells in cats. Then they examined the hidden processing layer and found that those "neurons" had rearranged their connections to approximate simple cells, complete with "on" and "off" regions in their receptive fields as well as directional sensitivity. In an earlier study, a neural network was trained to recognize curved visual objects (Lehky & Sejnowski, 1990). Its "neurons" spontaneously developed sensitivity to bars or edges of light even though they had never been exposed to such stimuli, suggesting that the Hubel-Wiesel model is a very versatile one.

But so far, Hubel and Wiesel had seen only the beginnings of the intricate neural organization that makes visual perception possible. They lowered electrodes perpendicularly through a monkey's striate cortex; as the electrode passed through simple and complex cells, the cells' preferred width and length changed, but they had the same orientation (Hubel & Wiesel, 1974). As the researchers moved the electrode slightly to the side, the preferred orientation of those cells shifted slightly but systematically in a clockwise or counterclockwise direction; over a distance of 0.5 to 1.0 mm, the orientation would progress through the complete circle. A complete 360-degree "set" of preferred orientations tends to be organized around a common point, forming what are called orientation pinwheels or whorls (Figure 10.25a and 10.25b;

Yacoub, Harel, & Ugurbil, 2008). This arrangement is repeated in the adjacent cortex, with the input coming from an adjacent part of the retina. This sort of organization is typical of the cortex's efficiency in processing and transmitting information. Connections mostly run up and down in columns, with much shorter lateral connections. In addition, similar functions are clustered together, increasing communication speed and reducing energy requirements.



Description

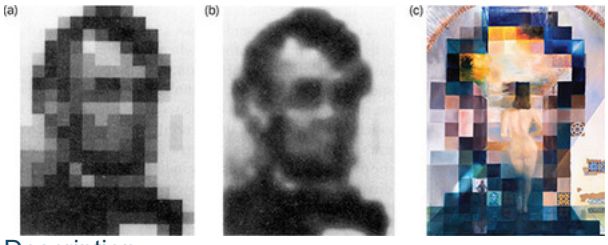
Figure 10.25 Orientations in Primary Visual Cortex.
(a) Preferred angle of a bar of light rotates around a fixed spot, forming what is called an orientation "pinwheel." (b) Orientation expressed as an angular graph. The colors are added to visualize the changes in orientation angle.

Hubel and Wiesel shared the Nobel Prize for their work in 1981. However, their model has limitations—some would say problems. For one thing, it accounts for the detection of boundaries, but it is questionable whether edge detection cells can also handle the surface details that give depth and character to an image.

Spatial Frequency Theory

Although some cortical cells respond best to edges (Albrecht, De Valois, & Thorell, 1980; De Valois, Thorell, & Albrecht, 1985; von der Heydt, Peterhans, & Dürsteler, 1992), other cells apparently are not so limited. Think of an edge as an abrupt or high-frequency change in brightness; the more gradual changes in brightness across the surface of an object are low-frequency changes. According to De Valois, some complex cells are "tuned" to respond to the high frequencies found in an object's border, while others are tuned to low frequencies, for example, in the slow transition from light to shadow that gives depth to the features of a face (De Valois et al., 1985). Some cells respond better to "gratings" of alternating light and dark bars—which contain a particular combination of spatial frequencies—than they do to lines and edges. According to **spatial frequency theory**, visual cortical cells do a Fourier frequency analysis of the luminosity variations in a scene (see Chapter 9 to review Fourier analysis). According to this view, different visual cortical cells have a variety of different sensitivities, not just those required to detect edges (Albrecht et al., 1980; De Valois et al., 1985).

A few photographs should help you understand what we mean by spatial frequencies, as well as the importance of low frequencies. The picture in Figure 10.26a was prepared by having a computer average the amount of light over large areas in a photograph; in other words, it's made up of large pixels. The result is a number of high-frequency transitions, and the image is not very meaningful. In Figure 10.26b, the computer filtered out the high frequencies, producing more gradual changes between light and dark (low frequencies). It seems paradoxical that blurring an image would make it more recognizable, but blurring eliminates the sharp boundaries. You can get the same effect from Figure 10.26a by looking at it from a distance or by squinting. Inspired by reading about the research in a *Scientific American* article, the Spanish artist Salvador Dalí incorporated the illusion into one of his more famous paintings (Figure 10.26c). A real-life example in Figure 10.27 suggests what our visual world might be like if we were limited to high frequencies or low frequencies.



Description

Figure 10.26 Illustration of High and Low Frequencies in a Visual Scene.
(a) An image limited to abrupt changes in brightness (high spatial frequencies) is not as meaningful as (b) one that has both high- and low-frequency information. The image in (b) is the same image as (a), except that the edges have been blurred. (c) Salvador Dalí's 1976 painting *Gala Contemplating the Mediterranean Sea Which at Twenty Meters Becomes a Portrait of Abraham Lincoln.* Look closely and you will see (a) rather than Dalí's wife Gala; squint your eyes and you will see (b).

Sources: (a) and (b) From "Masking in Visual Recognition: Effects of Two-Dimensional Filtered Noise," by L. D. Harmon and B. Julesz, *Science, 180,* pp. 1194–1197. Reprinted with permission from AAAS.
(c) Georg Berg / Alamy Stock Photo.

Figure 10.27 The Role of High and Low Frequencies in Vision.
(a) The original photo; (b) the same photo with low frequencies removed; (c) the photo with high frequencies removed. Notice how high-frequency changes in contrast define borders and fine details, while low frequencies reveal distinguishing characteristics through shadow and texture.

Source: © Bob Garrett.

? Is spatial frequency theory a better explanation?

So far, we have dealt only with the simplest aspects of visual perception. But we also are able to recognize an object as an object, assign it color under varied lighting conditions, and detect its movement. Attempting to explain these capabilities will provide challenge enough for the rest of this chapter.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- Explain how the opponent arrangement of a ganglion cell's field enhances brightness contrast.
- How did Hubel and Wiesel explain our ability to detect an edge, the orientation of an edge or a line, and an edge or a line that changed its location?
- How do Hubel and Wiesel's theory and the spatial frequency theory differ?

THE PERCEPTION OF OBJECTS, COLOR, AND MOVEMENT

One of the more interesting characteristics of the visual system is how it dissects an image into its various components and analyzes them in different parts of the brain. The separation begins in the retina and increases as visual information flows through all four lobes of the brain, with locations along the way carrying out analyses of color, movement, and other features of the visual scene. Thus, we will see how visual processing is, as mentioned earlier, both modular and hierarchical. **Modular processing** refers to the segregation of the various components of processing into separate locations. **Hierarchical processing** means that lower levels of the nervous system analyze their information and pass the results on to the next higher level for further analysis.

Some neuroscientists reject the modular notion, arguing that any visual function is instead **distributed**, meaning that it occurs across a relatively wide area of the brain. One study found evidence that sensitivity to faces, for example, is scattered over a large area in the temporal lobe (Haxby et al., 2001). Different studies have supported both of these views (J. D. Cohen & Tong, 2001), and it can be argued that vision involves a mix of modular and distributed functioning, rather like the arrangement we saw for language. In the following discussion, you will see that basic visual analysis occurs in isolated modules, and more comprehensive analysis is distributed across the width and breadth of the brain.

The Two Pathways of Visual Analysis

Most visual information follows two routes from the retina through the brain, which make up the *parvocellular system* and the *magnocellular system* (M. Livingstone & Hubel, 1988; P. H. Schiller & Logothetis, 1990). Parvocellular ganglion cells are smaller than magnocellular cells, account for the large majority of ganglion cells, and are most numerous in the fovea. They have circular receptive fields that are small and color opponent, which suits them for the specialties of the **parvocellular system**, the discrimination of fine detail and color. Magnocellular ganglion cells have large circular receptive fields that are brightness opponent and respond rapidly but only briefly to stimulation. As a result, the **magnocellular system** is specialized for brightness contrast and for movement.

? What do the parvocellular and magnocellular systems do?

We see evidence of differences in the two systems in our everyday lives. The simplest example is that at dusk our sensitivity to light increases, but we lose our ability to see color and detail. You cannot read a newspaper under such conditions or color coordinate tomorrow's outfit, because the high-resolution, color-sensitive parvocellular system is nearly nonfunctional. The magnocellular system's sensitivity to movement is most obvious in your peripheral vision. Hold your arms outstretched to the side while you look straight ahead, and move your hands slowly forward while wiggling your fingers. When you just notice your fingers moving, stop. Notice that you can barely see your fingers but you are very sensitive to their movement. Figure 10.28 is a striking demonstration of another capability of the magnocellular system, depth perception. Notice that you see considerable depth in (a); this is because the bicycle differs from the background in brightness, so the image stimulates primarily the magnocellular system. The bicycle in (b) looks "flat"; the image has color contrast but little brightness contrast, so it stimulates the magnocellular system minimally.

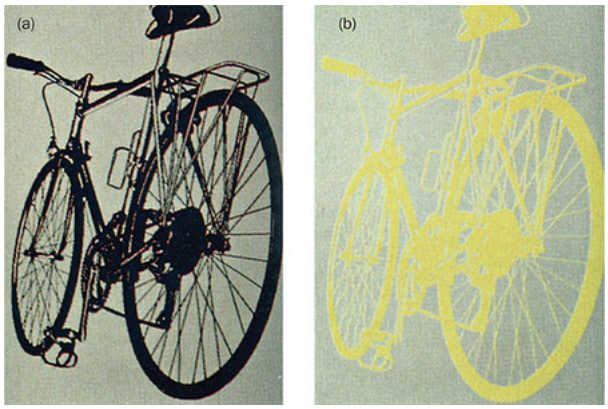
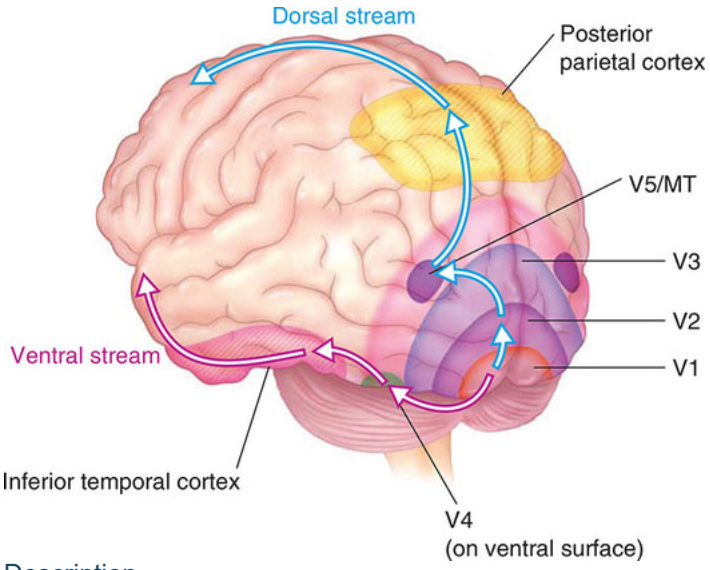


Figure 10.28 Color Contrast and Brightness Contrast Stimulate Different Visual Systems.
Image (a) has considerable brightness contrast, so it mostly stimulates the magnocellular system, giving an appearance of depth. Image (b) consists of color contrast, which provides little stimulation to the magnocellular system.

Source: From "Segregation of Form, Color, Movement, and Depth: Anatomy, Physiology, and Perception," by M. Livingstone and D. Hubel," *Science, 240*, pp. 740–749. Copyright 1988, Reprinted with permission from American Association for the Advancement of Science (AAAS).

? What are the functions of the ventral and dorsal streams?

Both pathways travel to the lateral geniculate nucleus and then to the primary visual cortex, which is also known as V1. Although the two systems are highly interconnected, the parvocellular system dominates the **ventral stream**, which flows from the visual cortex into the temporal lobes, and the magnocellular system dominates the **dorsal stream** from the visual cortex to the parietal lobes (Figure 10.29). Like the two auditory pathways, the ventral stream is often referred to as involved with the "what" of visual processing, and the dorsal stream with the "where." Most of the research on this topic has been done with monkeys, but the two pathways have been confirmed with PET scans in humans (Ungerleider & Haxby, 1994).



Description

Figure 10.29 The Ventral "What" and Dorsal "Where" Streams of Visual Processing.

Carolina Hrejsa/Body Scientific Intl.

Beyond V1, the ventral stream passes through V2 and into V4, whose various cells are tuned to color, brightness, texture, shape, motion, and depth (Roe et al., 2012). It then projects to the inferior temporal cortex, which is the lower boundary of the temporal lobe; this area shows a remarkable specialization for object recognition, which we will examine shortly.

Magnocellular neurons arrive in V1 in areas that are responsive to orientation, movement, and retinal disparity (Poggio & Poggio, 1984). The dorsal stream then proceeds through V2 to V5, also known as MT because it is on the middle temporal gyrus in the monkey; neurons there have strong directional sensitivity, which contributes to the perception of movement. The dorsal stream travels then to the posterior parietal cortex, the area just behind the somatosensory cortex; its role is primarily to locate objects in space, but the behavioral implications of its functions are far more important than that simple statement suggests.

Movement perception is a good example of how modular and distributed processing work together. V5/MT and a nearby area that receives input from MT, known as MST (for medial superior temporal area), appear to be the most important areas for perceiving movement. They receive most of their input from the magnocellular pathway, including complex cells that are sensitive to movement; they also respond when the motion is only implied in a photograph of an athlete in action or a picture of a cup falling off a table (Culham, He, Dukelow, & Verstraten, 2001). At the same time, there are many other areas that are specialized for particular kinds of movement. Viewing movement of the human body or its parts activates dorsal stream areas adjacent to V5/MT and MST, in the parietal and frontal lobes and in the ventral stream in the temporal lobes (Vaina, Solomon, Chowdhury, Sinha, & Belliveau, 2001; Wheaton, Thompson, Syngeniotis, Abbott, & Puce, 2004).

Images move across your retinas every time you move your eyes, but you don't see the world moving around you. (Imagine trying to read otherwise.) This is because the activity of movement-sensitive cells in MT and MST is suppressed during eye movements (Thiele, Henning, Kubischik, & Hoffmann, 2002). These cells are sensitive to movement in a particular direction, and some of them reverse their preferred direction of movement as the head moves, which allows them to continue responding to real movement of objects. The brain's visual movement areas are close to an area that processes input from the vestibular organs, which monitor body motion (Thier, Haarmeier, Chakraborty, Lindner, & Tikhonov, 2001); you are already indirectly familiar with this fact if you get motion sickness in a moving car when you read or when you watch roadside objects too closely.

The functions of the ventral "what" and dorsal "where" streams are best illustrated by a comparison of patients with damage in the two areas. People with damage in the temporal cortex (ventral stream) have trouble visually identifying objects, but they can walk toward or around the objects and reach for them accurately (Kosslyn, Ganis, & Thompson, 2001). People with damage to the dorsal stream have the opposite problem. They can identify objects, but they have trouble orienting their gaze to objects, reaching accurately, and shaping their hands to grasp an object using visual cues (Ungerleider & Mishkin, 1982). So the dorsal "where" stream also functions as a "how" area that is important for action.

From the parietal and temporal lobes, the dorsal and ventral streams both proceed into the prefrontal cortex. One function of the prefrontal cortex is to manage this information in memory while it is being used to carry out the functions that depend on the two pathways (Courtney, Ungerleider, Keil, & Haxby, 1997; F. A. Wilson, Ó Scalaidhe, & Goldman-Rakic, 1993). As one example, we will see in Chapter 11 that the prefrontal cortex integrates information about the body and about objects around it during the planning of movements.

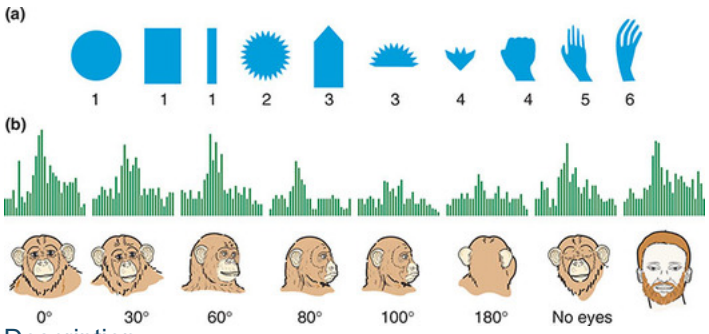
Disorders of Visual Perception

Because the visual system is somewhat modular, damage to a processing area can impair one aspect of visual perception while all others remain normal. This kind of deficit is often called an *agnosia*, which means “lack of knowledge.” Because the disorders provide a special opportunity for understanding the neural basis of higher-order visual perception, we will orient our discussion of the perception of objects, color, movement, and spatial location around disorders of those abilities.

Object and Face Agnosia

Object agnosia is impairment of the ability to recognize objects visually. In Chapter 3, we described Oliver Sacks’s (1990) agnosic patient who patted parking meters on the head, thinking they were children; he was also surprised when carved knobs on furniture failed to return his friendly greeting. Dr. P. was intellectually intact; he continued to perform successfully as a professor of music, and he could carry on lively conversations on many topics. Patients with object agnosia are able to see an object, describe it in detail, and identify it by touch. But they are unable to identify an object by sight or even to recognize an object from a picture that they have just drawn from memory (Gurd & Marshall, 1992; Zeki, 1992).

Object agnosia is caused by damage to the inferior temporal cortex (see Figure 10.29); this part of the ventral stream is where information about edges, spatial frequencies, texture, and so on is reassembled to form perceptions of objects. Cells have been located there in monkeys and humans that respond selectively to geometric figures, houses, animals, hands, faces, or body parts (Figure 10.30a; Desimone, Albright, Gross, & Bruce, 1984; Downing, Jiang, Shuman, & Kanwisher, 2001; Gross, Rocha-Miranda, & Bender, 1972; Kreiman, Koch, & Fried, 2000; Sáry, Vogels, & Orban, 1993). Some of these cells require very specific characteristics of a stimulus, such as a face viewed in profile; others continue to respond in spite of changes in rotation, size, and color (Figure 10.30b; Miyashita, 1993; Tanaka, 1996; Vogels, 1999). The latter group of cells likely receive their input from cells with narrower sensitivities (Tanaka, 1996), like those in V1 that detect edges. The inferior temporal cortex also has a columnar organization reminiscent of what we saw in V1; a column of object-responsive cells might respond to variations on a star-like shape, for example, and a column adjacent to one that responds to a frontal view of a face is activated by a face in profile (Tanaka, 2003).



Description

Figure 10.30 Stimuli Used to Produce Responses in Hand- and Face-Sensitive Cells in Monkeys.
(a) The stimuli are ranked in order of increasing ability to evoke a response in a hand-sensitive cell. (b) The spikes recorded from a face-sensitive cell indicate the degree of response from the stimulus shown below.

Sources: (a) From “Visual Properties of Neurons in Inferotemporal Cortex of the Macaque,” by C. G. Gross et al., 1972, *Journal of Neurophysiology, 35*. Reprinted with permission. (b) Adapted from Stimulus-selective properties of inferior temporal neurons in the macaque by R. Desimone, et al., p. 2057. in Journal of Neuroscience, 4, 1984.

Like Dr. P., many people with object agnosia also suffer from **prosopagnosia**, an impairment of the ability to visually recognize familiar faces. The problem is not memory, because they can identify individuals by other characteristics, such as their speech or mannerisms. Nor is their visual acuity impaired; they often have no difficulty recognizing facial expressions, gender, and age (Tranel, Damasio, & Damasio, 1988). However, they are unable to recognize the faces of friends and family members or even their own image in a mirror (Benton, 1980; A. R. Damasio, 1985). Prosopagnosia has a variety of causes, including stroke, carbon monoxide poisoning, and Alzheimer's disease. Damage usually impairs the ability to recognize both objects and faces, but the occasional case is reported of a patient with prosopagnosia alone (Benton, 1980) or of object agnosia with spared face identification (Behrmann, Moscovitch, & Winocur, 1994).

While some processing of face information occurs in the inferior temporal cortex, recognizing individual faces requires additional structures. In humans, a part of the fusiform gyrus located in the inferior temporal cortex is so important to face recognition that it is referred to as the **fusiform face area (FFA)**. This area begins assisting us in recognizing caregiver faces at about 2 years of age (Bushnell, 2001) but can be developmentally delayed in individuals with autism (Scherf, Behrmann, Minshew, & Luna, 2008). Damage that results in prosopagnosia is usually in the right hemisphere (Figure 10.31; Bouvier & Engel, 2006; Gauthier, Skudlarski, Gore, & Anderson, 2000; Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999), but face processing is a cooperative effort involving both sides of the brain. Face-like images produce activity in the left fusiform gyrus that is proportionate to the image's resemblance to a face; the right fusiform gyrus becomes active 2 two seconds later, only when the image is of a human face (M. Meng, Cherian, Singal, & Sinha, 2012). Another area that has been implicated in face recognition is the medial temporal lobe, which is important in memory and seems to be involved in decision making between familiar and unfamiliar faces (Quian Quiroga, Kraskov, Mormann, Fried, & Koch, 2014).

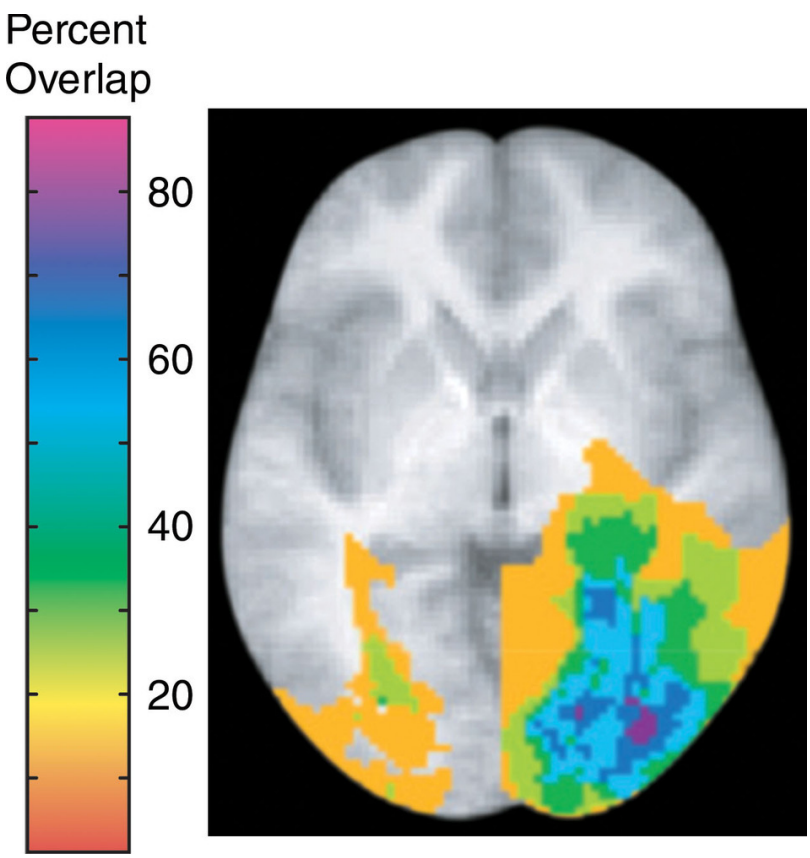
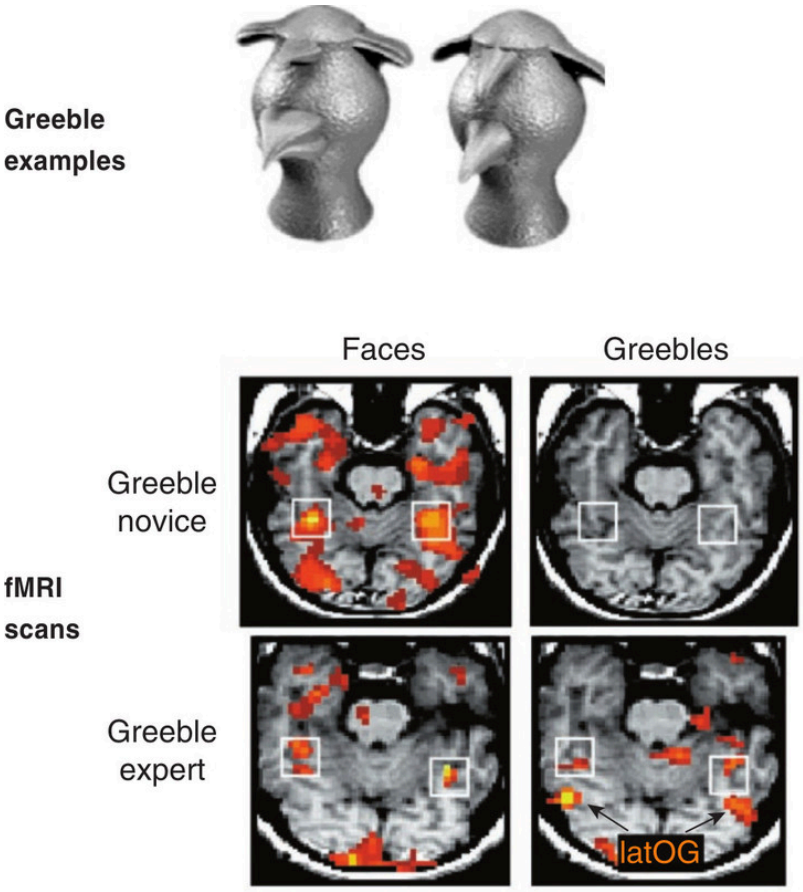


Figure 10.31 Location of Brain Damage in Patients With Prosopagnosia.
The color of the area indicates how often damage was observed there in patients with prosopagnosia.

Source: From "Behavioral Deficits and Cortical Damage Loci in Cerebral Achromatopsia," by S. E. Bouvier and S. A. Engel, 2006, *Cerebral Cortex, 16,* pp. 183–191, by permission of Oxford University Press.

Until fairly recently, researchers thought the only way prosopagnosia occurred was through brain damage. Then medical student Martina Grueter began to recognize the symptoms in her husband's behavior and made congenital prosopagnosia the subject of her MD thesis (Grueter, 2007). An estimated 2.5% of the population has symptoms of the disorder without any history of brain damage (Kennerknecht et al., 2006); thus, they make errors in recognizing familiar faces, and they learn new faces slowly (Grüter, Grüter, & Carbon, 2008). Afflicted individuals include noted primatologist Jane Goodall, actor Brad Pitt, and Oliver Sacks, the neurologist who studied Dr. P. Face recognition ability has a heritability of about 39% (Zhu et al., 2010), so its deficiency in the absence of brain damage likely has a genetic origin. The defect, though, does not appear to be in the fusiform face area itself; the FFA responds normally, but connections to more anterior temporal and frontal cortex areas are diminished (Avidan & Behrmann, 2009). This suggests that face recognition is a distributed function, despite modularity of its components.

These capabilities might be "hardwired" at birth to some extent, but they also are amenable to learning. When researchers showed monkeys pictures of the faces of lab workers, neurons in the inferior temporal cortex increased their firing rates according to the monkeys' familiarity with the workers (M. P. Young & Yamane, 1992). Isabel Gauthier and her colleagues (1999) trained humans to identify faces, using pictures of fictitious creatures they called "greebles" to ensure initial unfamiliarity. The fMRI scans in Figure 10.32 show that pictures of human faces activated the FFA, but greebles did so only after the person had learned to recognize individual creatures.



Description

Figure 10.32 Activity in the Fusiform Face Area While Viewing Faces and "Greebles." Viewing faces activated a part of the fusiform gyrus (indicated by the white squares) both in "greeble novices" and in "greeble experts," who had learned to distinguish individual greebles from each other. Viewing greebles activated the area only in greeble experts. (Red indicates more activation than yellow.)

Source: From "Activation of the Middle Fusiform 'Face Area' Increases With Expertise in Recognizing Novel Objects," by I. Gauthier et al., *Nature Neuroscience, 2,* pp. 568–573. © 1999 Nature Publishing Group.

People with prosopagnosia do respond emotionally to photographs of familiar faces they do not recognize, as indicated by EEG-evoked potentials and skin conductance response (R. M. Bauer, 1984; Renault, Signoret, Debruille, Breton, & Bolger, 1989; Tranel & Damasio, 1985). This "hidden perception" is not without precedent. Patients blinded by damage to V1 show a surprising ability to track the movement of objects and discriminate colors, all the while claiming to be guessing (Zeki, 1992). Cortically blind individuals also can identify emotions expressed in faces they do not otherwise see (Tamietto et al., 2009), and they can avoid obstacles while walking. This ability to respond to visual stimuli that are not consciously seen is called **blindsight**. Imaging studies have found that blindsight depends on pathways passing through the superior colliculus directly to extrastriate areas, bypassing V1 (reviewed in de Gelder & Tamietto, 2007; Tamietto et al., 2010).

An area in the inferior temporal cortex near the FFA has an intriguingly similar "object" recognition function; the **visual word form area (VWFA)** responds to written words as a whole. Its importance in reading was demonstrated in a patient whose VWFA was disconnected from adjacent language areas by surgery undertaken to remove tissue that was causing epileptic seizures (Gaillard et al., 2006). Before surgery, the patient could recognize familiar words of any length in less than a second; following

surgery, the time had almost doubled for three-letter words and increased by an additional 100 milliseconds for each additional letter, indicating that he was deciphering words letter by letter. Performance in identifying faces, tools, and houses was unaffected. The VWFA is typically underactivated in adults with dyslexia during reading (McCandliss & Noble, 2003), but, consistent with what we saw in Chapter 9, the authors suggest that this is not the cause of the dyslexia but the result of phonological deficits that interfere with learning rapid word recognition. It is clear that the VWFA could not have evolved as a dedicated whole-word detector, because written language is a relatively recent invention; still, it serves that function so precisely that two words evoke activity in different subareas, even when the words differ by just one letter (Glezer, Jiang, & Riesenhuber, 2009). What is intriguing about the VWFA is that, for whatever reason, the area has evolved special capabilities that suit it for learning to identify words as if they are unique visual "objects."

Color Agnosia

Let's return to Jonathan I., whose plight was described at the beginning of the chapter. Jonathan's problem was **color agnosia**, which is the loss of the ability to perceive colors due to brain damage. But before we can discuss this disorder, we need to revisit the distinction between wavelength and color. As one of the authors walked past a colleague's slightly open office door, he was astonished to see that his colleague's face was a distinct green! Opening the door to investigate, he understood why: The light from the colleague's desk lamp was reflecting off a bright green brochure he was reading. Immediately his face appeared normal again. This ability to recognize the so-called natural color of an object despite variations in brightness and wavelength of illumination is called **color constancy**. An example of this can be seen in Figure 10.33. The tiles that are in shadow or illuminated by a red light reflect different wavelengths, but they do not seem altered to the viewer; they appear to be the same colors as the tiles on the top and right sides of the first cube. If not for color constancy, objects would seem to change colors as the sun shifted its position through the day or as we went indoors into artificial (or colored) light. Imagine having to survive by identifying ripe fruit if the colors kept changing.

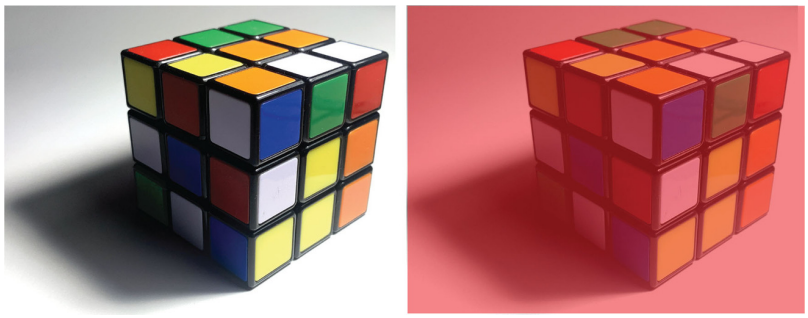


Figure 10.33 Color Constancy.
Variations in the brightness (shadowing on the left) or color of illumination (red ambient light on the right) will cause a shift in the stimulation reaching the eye, but the viewer will experience colors as much the same.

? How is color coding different from wavelength coding?

When the author reinterpreted his colleague's skin color, it was not because he *understood* that his friend's face was bathed in green light; it occurred automatically as soon as his eyes took in the whole scene. Monkeys, who do not understand the principles of color vision, apparently have the same experience. When Zeki (1983) illuminated red, white, green, and blue patches with red light, each patch set off firing in V1 cells that preferred long-wavelength (red) light, regardless of its actual color; however, cells in V4 responded only when the patch's actual color matched the cell's color "preference." Zeki concluded that cells in V1 are *wavelength coded*, whereas cells in V4 are *color coded*. Schein and Desimone (1990) suggested how V4 cells

provide color constancy. They have large circular receptive fields that are color opposed; so if, for example, a green light falling on the center increases the cell's firing rate, green light falling simultaneously in the surround reduces or eliminates the increase. In other words, the cells "subtract out" the color of any general illumination. The cortical cells required to do this have been confirmed in monkeys (Conway and Livingstone, 2006).

We have no brain scan to tell us where Jonathan I.'s damage was located, but we know that cortical color blindness, or *cerebral achromatopsia*, occurs when people have lesions between V1 and the FFA (Heywood & Kentridge, 2003; Witthoft et al., 2013); this is where V4 is located, but it is unclear whether the deficiency can be attributed to V4 malfunction. Unlike Jonathan I., many patients are unaware their color vision is impaired, just as we saw in Chapter 9 with Wernicke's aphasia.

Movement Agnosia

Although movement is detected by neurons in V1 and beyond, area V5/MT is the place where that information is integrated; MT (for middle temporal area) also helps direct reaching movements and eye movements when tracking objects (Born & Bradley, 2005; Whitney et al., 2007). A 43-year-old woman known in the literature as L. M. suffered a stroke that caused bilateral damage in the general area of MT; the result was **movement agnosia**, impairment of the ability to detect movement (Vaina, 1998; Zihl, von Cramon, & Mai, 1983). Although her vision was otherwise normal, she could distinguish between moving and stationary objects only in her peripheral view, and she had trouble detecting the movement of people if there were more than two people in the room. She was often surprised when an object had changed position, because she had no sense of the object traveling through the intermediate positions (Zihl et al., 1983). When she tried to cross a street, a car would seem far away, but then suddenly very near. Similarly, when she poured coffee, she could not tell that the liquid was rising in the cup, so she would keep pouring until the cup overflowed!

Later analyses indicated that L. M.'s most severe impairment was in her ability to detect radial movement (Vaina, 1998). We experience radial movement when the image of an approaching car expands outwardly, or radially. Radial movement also tells us that we are approaching an object when we walk or drive, because all the environmental objects around the central point appear to move outward; this effect provides information about our *heading* and is important for personal navigation. A patient with impaired perception of radial movement could not catch a ball that was thrown to him, and he frequently bumped into people in his wheelchair. Scans done while subjects perform a task involving radial movement or heading detection implicate the MST area (for medial superior temporal area, where it is located), which receives its input from MT (Peuskens, Sunaert, Dupont, Van Hecke, & Orban, 2001; Vaina, 1998).

Visuospatial Neglect and the Role of Attention in Vision

The posterior parietal cortex combines input from the visual, auditory, and somatosensory areas to help the individual locate objects in space and to orient the body in the environment. Damage impairs abilities such as reaching for objects, but it also often produces *neglect*, in which the patient ignores visual, touch, and auditory stimulation on the side opposite the injury. The term *neglect* seems particularly appropriate in patients who ignore food on the left side of the plate, shave only the right side of the face, or fail to dress the left side of the body. Neglect is twice as likely following right-hemisphere stroke, occurring in 40% of cases compared to 20% of left-hemisphere stroke (Zebhauser, Vernet, Unterburger, & Brem, 2019). The manifestations are largely, but not entirely, visuospatial. Visuospatial neglect shows up even when a patient is asked to describe a remembered or imagined scene. The mechanism is unclear; some studies suggest an inability to mentally represent the information from the neglected side, while others point to an attentional deficit due to the intact hemisphere directing attention to the non-neglected side.

Patients' drawings and paintings help us understand what they are experiencing. When asked to copy drawings, they will neglect one side while completing the other side in detail, (see Figure 10.34). The two portraits in Figure 10.35 were painted by Anton Raderscheidt 2 and 9 months after a stroke that damaged his right parietal area. Notice that the first painting has very little detail, and the left half of the image is missing. In the later painting, he was using the whole canvas, and the portrait looks more normal, but notice that the left side is still much less developed than the right, with the eyeglasses and face melting into ambiguity (R. Jung, 1974).

Description

Figure 10.34 What a Left-field Neglect Patient Perceives.

Source: Schwartz, B. L. & Krantz, J. H. (2015).

Figure 10.35 Self-Portraits Demonstrating Left Visual Field Neglect.
(a) A self-portrait done 2 months after the artist's stroke, which affected the right parietal area, is incomplete, especially on the left side of the canvas. (b) One done 9 months after the stroke is more complete but still shows less attention to detail on the left side.

© 2020 Artists Rights Society (ARS), New York / VG Bild-Kunst, Bonn

The Problem of Final Integration

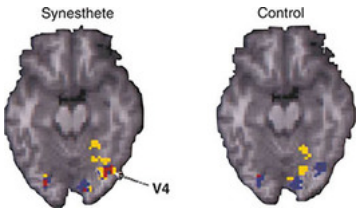
We have seen how the brain combines information about some aspects of an object, but many researchers wonder where *all* the information about the object is brought together; how the brain combines information from different areas into a unitary whole is known as the **binding problem**. Imagine watching a person walking across your field of view; the person is moving, shifting orientation, and changing appearance as the lighting increases and decreases under a canopy of trees. At the same time, you are walking toward the person, but your brain copes easily with the changing size of the person's image and the apparent movement of environmental objects toward you. It seems logical that a single center at the end of the visual pathway would combine all the information about shape, color, texture, and movement, constantly updating your perception of this image as the same person. In other words, the result would be a complete and dynamic awareness. Presumably, damage to that area would produce symptoms that are similar to blindsight but that affect all stimuli.

It has been suggested that our ultimate understanding of an object occurs in a part of the superior temporal gyrus that receives input from both neural streams (Baizer, Ungerleider, & Desimone, 1991) or in the part of the parietal cortex where damage causes neglect (Driver & Mattingley, 1998). Other investigators suspect frontal areas where both streams converge. But these ideas are highly speculative, and there is no convincing evidence for a master area where all perceptual information comes together to produce awareness (Crick, 1994; Zeki, 1992). The variety of hypothesized awareness centers suggests another possibility, that visual awareness is *distributed* throughout the network of 32 areas of cortex concerned with vision and their 305 interconnecting pathways (Van Essen, Anderson, & Felleman, 1992). This thinking is exemplified on a small scale in the interaction between V5/MT and V1. After a stimulus occurs, activity continues back and forth between these areas for a few hundred milliseconds, and disrupting this interchange eliminates awareness of movement (reviewed in McKeefry, Gouws, Burton, & Morland, 2009).

Actually, the brain's task is a balancing act between combining relevant information and segregating unrelated or inconsequential information. A Further Look illustrates this point by describing **synesthesia**, a condition in which stimulation in one sense triggers an experience in another sense or a concept evokes an unrelated sensory experience. We will spend more time examining how the brain sorts out and uses information when we talk about consciousness in Chapter 15.

A Further Look:

When Binding Goes Too Far



Spoken words activate left-hemisphere area V4 in a synesthete but not in a control. Why do you think this activity occurred mostly in the left hemisphere?

Source: From "Functional Magnetic Resonance Imaging of Synesthesia: Activation of V4/V8 by Spoken Words," by J. A. Nunn et al., 2002, *Nature Neuroscience, 5,* pp. 371–375.

Before his accident, Jonathan I. saw a "tumult" of changing colors whenever he listened to music. For other people with synesthesia, letters may have colors, days of

the week may have personalities, visual motion might produce sounds, or words might have tastes. More than 60 varieties of synesthesia have been documented, and most synesthetes report more than one form (Brang & Ramachandran, 2011). Synesthesia was thought to be rare, based on the number of people who came forward to report these experiences, but when Julia Simner and her colleagues (2006) tested 1,700 non-self-referred individuals, almost 5% showed characteristics of synesthesia. One third of those were projectors, who experience the unrelated color or sound or taste, and the rest were associators, who actually have a persistent mental association between, for example, a word and a color but don't report that they see the color. Synesthesia is a neurological phenomenon; fMRI studies show that area V4 is active when grapheme/color synesthetes view letters and numbers and when auditory word/color synesthetes listen to spoken words (see figure; Hubbard, Arman, Ramachandran, & Boynton, 2005; Nunn et al., 2002).

There are two competing hypotheses as to why synesthetes "overbind" sensory information: Either there is excess connectivity among the involved brain areas, or there is inadequate inhibition in otherwise normal pathways. Studies favor the connectivity hypothesis; a diffusion tensor imaging MRI study (suited for imaging white matter) indicated that grapheme/color synesthetes had more pronounced connections in the inferior temporal, parietal, and frontal cortex—all areas involved in processing and integrating visual information (Rouw & Scholte, 2007). Genetic studies suggest that synesthesia runs in families, and at least four of the five chromosomal areas implicated contain genes for axon guidance and cortical development (Asher et al., 2009; S. N. Thomson et al., 2011).

By all rights, synesthesia could be considered a developmental brain disorder, but other than being a bit of a distraction, it is relatively benign, and, like Jonathan I., many synesthetes enjoy their enriched sensory experience. Besides, they often have no idea they are different from others. Julian Asher, who led the genetic study described above, discovered his synesthesia when, as a child attending the symphony with his parents, he remarked, "Oh, they turned the lights off so you could see the colors" (Landau, 2000).

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- Explain why higher-order processing is required to recognize the natural color of objects; how does it work?
- Draw a diagram of the brain, add lines showing the two major visual pathways, and label the various areas; for the higher-order processing areas, include their functions.

IN PERSPECTIVE

Very few subjects in the field of behavioral neuroscience can match the interest that researchers have bestowed on vision. As a result, we know more about the neuroanatomy and functioning of vision than any other neural system. Still, many challenges remain in the field of vision research.

Researchers' fascination with vision goes beyond the problems of vision itself. Our understanding of the networks of neurons and structures in the visual system provides a basis for developing theories to explain other functions as well, including the integration of complex information into a singular awareness. Whatever directions future research might take, you can be sure that vision will continue to be one of the most important topics.

Chapter Summary

Light and the Visual Apparatus

- The human eye is adapted to the part of the electromagnetic spectrum that is reflected from objects with minimal distortion. Color is related to the wavelength of light but is not synonymous with it.
- The retina contains rods, which are specialized for brightness discrimination, and cones, which are specialized for detail vision and discrimination of colors. The cells of the retina are highly interconnected to carry out some processing at that level.
- The optic nerves project to the two hemispheres so that information from the right visual field goes to the left visual cortex, and vice versa.

Color Vision

- There are three types of cones, each containing a chemical with peak sensitivity to a different segment of the electromagnetic spectrum.
- Connections of the cones to ganglion cells provide for complementary colors and for perception of yellow as a unique color.
- The most common cause of partial color blindness is the lack of one of the photopigments.

Form Vision

- Form vision begins with contrast enhancement at edges by ganglion cells with light-opponent circular fields.
- These ganglion cells contribute to cortical mechanisms that detect edges (Hubel and Wiesel’s theory) or that perform a Fourier analysis of a scene (spatial frequency theory).

The Perception of Objects, Color, and Movement

- Most visual information follows two somewhat separate paths through the brain, which are part of the magnocellular and parvocellular systems.
- Structures along the way are specialized for different functions, including color, movement, object perception, and face perception.
- We do not know how or where the components of vision are combined to form the perception of a unified object. One suggestion is that this is a distributed function.

Study Resources

For Further Thought

- Red and green are complementary colors and blue and yellow are complementary because their receptors have opponent connections to their ganglion cells. How would you explain the fact that bluish green and reddish yellow (orange) are also complementary?
- Considering what you know about the retina, how would you need to direct your gaze to read a book or to find a very faint star?
- Explain why the visual system analyzes an object's edges, texture, and color and then detects the object, instead of the other way around.
- Are Hubel and Wiesel's theory and the spatial frequency theory opposed or complementary theories?
- Cones in the bird retina detect blue, green, red, and ultraviolet. Can you imagine what they might gain from detecting ultraviolet reflections from objects in their environment? Then check http://en.wikipedia.org/wiki/Bird_vision (see the section "Ultraviolet Sensitivity"); you might be surprised by some of the benefits!
- How could you design traffic signs, uniforms, and safety equipment to make them recognizable to individuals with color vision deficiencies?

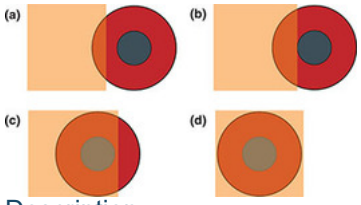
Test Your Understanding

1. Summarize the trichromatic and Hurvich-Jameson theories, indicating what facts about color vision each accounts for.
2. Compare the specialized sensitivities of simple and complex visual cortical cells; describe the interconnections among ganglion cells, simple cells, and complex cells that account for their specializations (according to Hubel and Wiesel).
3. The visual system can be described as modular, hierarchical, and distributed. What does this mean? (Use examples to illustrate.)

Select the best answer:

1. The receptive field of a cell in the visual system is the part of the ____ from which the cell receives its input.
    1. external world
    2. retina
    3. temporal lobe
    4. cortex
2. Mixing red and green lights produces a sensation of yellow because red-sensitive and green-sensitive cones
    1. excite yellow/blue ganglion cells.
    2. have opposite effects at yellow/blue ganglion cells.
    3. excite red/green ganglion cells.
    4. have opposite effects at red/green ganglion cells.
3. If our experience of color were entirely due to the wavelength of light reflected from an object, we would not experience
    1. complementary colors.
    2. the color yellow.
    3. primary colors.
    4. color constancy.
4. The parvocellular system is specialized for
    1. fine detail and movement.
    2. color and fine detail.
    3. color and movement.
    4. movement and brightness contrast.

5. What would be the effect on vision if there was a problem with your horizontal cells?
    1. Impaired color vision
    2. Detection of shapes in a complex background
    3. Impaired edge detection in the Mach band illusion
    4. Impaired night vision, but intact day vision
6. Cutting the optic nerve between the right eye and the chiasm would cause a loss of vision in
    1. the left visual field.
    2. the right visual field.
    3. half of each visual field.
    4. neither field, due to filling in.
7. People with red-green color blindness
    1. cannot see either red or green.
    2. see red and green as black.
    3. confuse red and green because they lack either “red” or “green” cones.
    4. confuse red and green because they lack one of the photopigments.
8. A light edge has enhanced apparent brightness next to a dark edge because the neurons activated by the light edge are inhibited
    1. less by their “dark” neighbors.
    2. more by their “dark” neighbors.
    3. less by their “light” neighbors.
    4. more by their “light” neighbors.
9. The ability of complex visual cortical cells to track an edge as it changes position appears to be due to
    1. input from receptors with similar fields.
    2. input from ganglion cells with similar fields.
    3. input from simple cells with similar fields.
    4. input from other complex cells.
10. According to the spatial frequency theory of visual processing, edges are detected by
    1. line-detecting cells in the visual cortex.
    2. edge detectors located in the visual cortex.
    3. cells that respond to low spatial frequencies.
    4. cells that respond to high spatial frequencies.
11. The circles represent the receptive field of a ganglion cell; the rectangle represents light. Unlike the illustrations in this chapter, the receptive field has an *off center*. In which situation will the ganglion cell’s rate of firing be greatest?



Description

12. Studies of object, color, and movement agnosias indicate that
    1. the visual system is unstable and malfunctions with no apparent cause.
    2. components of the visual image are processed separately.
    3. color, object identification, and movement information are integrated in one place.
    4. all functions are processed in one place but the results are distributed to other parts of the brain.
13. Movement perception is the primary function in visual area
    1. V1.
    2. V2.
    3. V4.
    4. V5.
14. A person who has trouble identifying objects visually probably has damage in the
    1. temporal lobe.
    2. parietal lobe.
    3. occipital lobe.
    4. frontal lobe.

Answers:

1. b, 2. a, 3. d, 4. b, 5. c, 6. c, 7. d, 8. a, 9. c, 10. d, 11. b, 12. b, 13. d, 14. a.

For Further Reading

1. “The Case of the Colorblind Painter,” by Oliver Sacks (in Sacks’s *An Anthropologist on Mars*, 1995, Vintage Books), is a compelling narrative of the case of Jonathan I.
2. “Visual Object Recognition: Do We (Finally) Know More Now Than We Did 20 Years Ago?” by Isabel Gauthier and Michael Tarr (*Annual Review of Vision Science*, 2016, *2*, 377–396) updates research on how we continue to recognize an object in spite of changes in orientation, lighting, and the like; “The Functional Neuroanatomy of Human Face Perception,” by Kalanit Grill-Spector, Kevin Weiner, Kendrick Kay, and Jesse Gomez (*Annual Review of Vision Science*, 2017, *3*, 167–196), reviews recent research on the ventral face network; and “Neuronal Mechanisms of Visual Attention,” by John Maunsell (*Annual Review of Vision Science*, 2015, *1*, 373–391), marshals recent research to provide a clearer understanding of how representations in the visual system change as attention shifts from one target to another.
3. *Vision and Art*, by Margaret Livingstone (2014, Harry N. Abrams, Publisher), explores how great painters use the science of vision to fool the brain with Mona Lisa’s mysterious smile and Monet’s swaying *Poppy Field*.
4. *Champions of Illusion: The Science Behind Mind-Boggling Images and Mystifying Brain Puzzles*, by Susana Martinez-Conde and Stephen Macknik (2017, Scientific American/Farrar, Straus and Giroux) is a book full of illusions illustrating brightness, contrast, color, size, shape, motion, perspective, and depth, along with scientific explanations.

Key Terms

accommodation 316

binding problem 345

blindsight 342

color agnosia 342

color blindness 327

color constancy 343

complementary colors 321

complex cell 333

distributed 337

dorsal stream 338

electromagnetic spectrum 314

form vision 328

fovea 317

fusiform face area (FFA) 341

hierarchical processing 337

iodopsin 317

lateral inhibition 329

magnocellular system 337

modular processing 337

movement agnosia 343

negative color aftereffect 321

object agnosia 340

opponent process theory 321

parvocellular system 337

photopigments 316

prosopagnosia 341

receptive field 317

retina 316

retinal disparity 319

retinotopic map 328

rhodopsin 317

simple cell 333

spatial frequency theory 335

synesthesia 345

trichromatic theory 321

ventral stream 338

visual acuity 317

visual field 319

visual word form area (VWFA) 342

Descriptions of Images and Figures

Back to Figure

The electromagnetic waves in the spectrum, from lowest wavelength to highest wavelength, are as follows.

- Gamma rays
- X-rays
- Ultraviolet rays
- Visible light between 380 nanometers and 760 nanometers, approximately. The approximate wavelength of the colors in visible light, in nanometers, are as

follows. Purple: 360 to 410. Blue: 420 to 480. Green: 490 to 550. Yellow: 560 to 600. Orange: 610 to 650. Red: Above 650.

- Infrared rays
- Radar
- F M
- Analog T V
- A M
- A C circuits

Back to Figure

The eye consists of the cornea forming a curved layer over the iris. The pupil is posterior to the iris, and the lens is posterior to the pupil. Ciliary muscles hold the lens in place and control it. Retina is at the back of the eye consisting of a notch labeled fovea or point of focus. The optic nerves extend away from the retina and a blind spot is on the retina at the origin of the optic nerves. Sclera forms a layer around the eye. Rays from a pencil, with its writing tip pointing downward, converge at the lens, diverge, and hit the retina, forming a smaller, curved, and inverted image. A magnified view of the retinal layer shows the following structures from the surface to the back of the eye: Ganglion cells, bipolar cells, and receptors such as rods and cones.

Back to Figure

1. Object far—eye relaxed: Parallel rays from a distant object pass through the cornea and the lens and converge at the fovea. The lens is relaxed and flat.
2. Object near—eye accommodation: Diverging rays from a near object pass through the cornea and the lens and converge at the fovea. The lens is rounded.

Back to Figure

Object A is on the left and object B is on the right. Object A casts an image on the right side of each retina and object B casts an image on the left side of each retina. The information is transmitted through the optic nerve till the optic chiasm. Then, information related to object A is transmitted through the lateral geniculate nucleus in the right hemisphere to the right visual cortex, and information related to object B is transmitted through the lateral geniculate nucleus in the left hemisphere to the left visual cortex.

Back to Figure

The image of object A falls on the fovea. The image of object B, located farther from the eyes than object A, falls on the medial side of the retina. The image of object C, located closer to the eyes than object A, falls on the lateral side of the retina.

Back to Figure

The top back left corner of the cube shows shades of green, the top front left corner shows shades of yellow, the bottom front left corner shows shades of red, the bottom front right corner shows shades of purple, the top front right corner shows white and is labeled 100 percent, and the back right corner shows shades of blue. An arrow labeled green points upward from bottom front left corner to top front left corner. An arrow labeled blue points to the right from bottom front left corner to bottom front right corner. An arrow labeled red points from the bottom back right corner to bottom front right corner.

Back to Figure

The colors in the wheel, starting from the top and going in clockwise direction, are as follows.

- First segment: Red.
- Fifth segment: Yellow.
- Eighth segment: Green.
- Tenth segment: Teal.
- Thirteenth segment: Blue.
- Fourteenth segment: Purple.

Back to Figure

The first Venn diagram shows the combination of colored lights. The combinations are as follows.

- Red and blue: Cyan.
- Blue and green: Dark violet.
- Green and red: Orange.
- Red, green, and blue: White.

The second Venn diagram shows the combination of colored lights. The combinationa are as follows.

- Red and blue: Cyan.
- Blue and green: Dark blue.
- Green and red: Pale orange.
- Red, green, and blue: Black.

Back to Figure

The three cone receptors are red, green, and blue. The two ganglion cells are red-green and yellow-blue.

- Red receptors activate both the ganglion cells.
- Green receptors activate yellow-blue cells and inhibit red-green cells.
- Blue receptors inhibit yellow-blue cells.

Back to Figure

The horizontal axis is labeled wavelength in nanometers, and ranges from 400 to 650 in increments of 50. The vertical axis is labeled percentage of maximum light absorption, and ranges from 0 to 100 in increments of 25. All data are approximate. The curve corresponding to blue cone at 420 nanometers starts from (370, 80), peaks at (400, 100), and falls to (520, 5). The curve corresponding to green cone at 534 nanometers starts from (380, 35), peaks at (525, 100), and falls to (645, 5). The curve corresponding to red cone at 564 nanometers starts from (385, 35), peaks at (555, 100), and falls to (660, 5). The curve corresponding to rods at 498 nanometers starts from (380, 30), peaks at (490, 100), and falls to (595, 5).

Back to image

1. An illustration shows a camera mounted on the center of a pair of goggles. An antenna and a processor are connected to the goggles. Signals emitted by the antenna attached to the goggles reach the antenna connected to the receiver that is attached to the electrode array inserted into the retina.
2. An image shows an electrode array in the retina.
3. A radiograph shows a coil mounted on the scalp behind the ear.

Back to Figure

The red cones respond to red color, the green cones respond to green color, the blue cones respond to blue color, and red and green cones respond to yellow color. The cones in the center activate the ganglion cell and cones in the periphery inhibit the cell.

- Red cones are in the center, and green cones are in the periphery.
- Green cones are in the center, and red cones are in the periphery.
- Red and green cones are in the center, and blue cones are in the periphery.
- Blue cones are in the center, and red and green cones are in the periphery.

Back to Figure

1. Normal vision: A photo of red, green, and yellow parrots perched on a branch.
2. Deuteranomaly: The photo of the parrots is less vivid and in shades of brown.
3. Protanopia: The photo of the parrots is in shades of green. The red parrot appears dark green.
4. Tritanopia: The photo of the parrots is in shades of pink. The green and yellow parrots appear pink.
5. The Ishihara test shows a circular cluster of orange and red dots, with green dots of different shades forming the number 74 within the cluster.

Back to Figure

1. An illustration shows four rows of black squares, with four squares in each row.
2. An illustration shows a band divided into four equal sections. Each section is depicted in a different shade of gray. The shade of gray increases from left to right. From the left, the second section is labeled A, the intersection of the second and third sections is labeled B, and the third section is labeled D.
3. In a graph, the horizontal axis is labeled distance, and the vertical axis is labeled light intensity ranging from low to high. A line starts from a point on the vertical axis corresponding to high value. At A and B, the intensity is high, and at C and D, the intensity is low.
4. In a graph, the vertical axis is labeled perception of lightness ranging from low to high. A curve starts from a point on the vertical axis corresponding to high value. The perception of lightness is high at point A, very high at point B, very low at point C, and low at point D.

Back to image

1. Three circles, each with a missing sector, are positioned such that they form the vertices of a triangle. V-shaped lines are between each circle and they open into the space enclosed within the circles. The sectors appear to enclose the vertices of a triangle.
2. An image shows four segmented circles. The colors of the segments are yellow, blue, black, and white, and the circles appear to rotate.
3. A drawing of an elephant that appears to have more than four legs.

Back to Figure

The stimulus is a band consisting of two equal sections: a light gray area and a dark gray area. There are fifteen numbered receptors, in which receptors 1 through 7 correspond to the light area of the stimulus and the give strong signals. Receptors 8 through 15 correspond to the dark area and give weak signals. There are fifteen numbered ganglion cells. Each cell receives a stimulating signal from its corresponding receptor and inhibiting signals from two receptors: one located to the left of its corresponding receptor and the other located to the right. Ganglion cell 7 is stimulated the most, ganglion cell 8 is inhibited the most, and ganglion cells 1 through 6 are stimulated more than ganglion cells 9 through 15. What the individual experiences as a result of this is represented by a band divided into four unequal sections. The first section corresponds to cells 1 through 6 and is light, the second section corresponds to cell 7 and is very light, the third section corresponds to cell 8 and is very dark, and the fourth section corresponds to cell 9 and is dark.
Back to Figure

Multiple cone receptors are connected to the ganglion cells. In both types of ganglion cells, the light producing inhibition strikes the receptors in the center, and the light producing excitation strikes in the periphery. In an on-center ganglion cell, the light producing inhibition stimulates the receptors. In an off-center ganglion cell, the light producing excitation stimulates the receptors.

Back to Figure

Each illustration shows the stimulus introduced to a ganglion cell and is accompanied by a blue bar consisting of vertical marks to indicate the neural responses.

1. In an on-center ganglion cell, a rectangle of light forms a layer completely over the receptors. There are four neural responses when the light was on.
2. In an on-center ganglion cell, a rectangle of light forms a layer over a portion of the periphery receptors. There are no neural responses when the light was on.
3. In an on-center ganglion cell, a rectangle of light forms a layer over a portion of the periphery receptors and over the receptors in the center. Neural responses occur at high frequency when light is on.
4. In an off-center ganglion cell, a dark object forms a layer over a portion of the periphery receptors and over the receptors in the center. Neural responses occur at high frequency in the presence of the dark image.

Back to Figure

The illustration shows five orientations of a line and their corresponding neural response in the presence of the line. The orientation of the line and the response are as follows.

- The line is horizontal. There are no responses.
- The line is inclined down to the right. There are two responses.
- The line is vertical. There are five responses.
- The line is inclined up to the right. There are two responses.
- The line is shifted downward. There are four responses.

Back to Figure

The illustration shows the receptive fields in a retina depicted by a column of five dots centered at a circle each. The circles overlap each other. Each field is connected to a ganglion cell, and the ganglion cells are connected to a single simple cell. An upright rectangular layer of light covers the left side of the receptive fields and the circles in the field.

Back to Figure

The illustration shows the receptive fields in a retina depicted by five rows of dots, with three dots in each row centered at a circle each. The edges of the dots touch one other, and the circles overlap each other. The fields on the left side are connected to a simple cell, and the fields on the right side are connected to another simple cell. The simple cells are connected to a complex cell, which in turn is connected to the middle field in the last row. An upright rectangular layer of light covers the first two columns of dots, the receptors on the left side, the left and middle portions of the receptors in the middle, and the left side of the receptors on the right side.
Back to Figure

1. A square consists of a black dot in the center. It is divided into six segments by curved lines originating from the dot in the center. Each segment consists of a rectangle. In each successive segment in the clockwise direction, the rectangle rotates clockwise.
2. The base of a semicircle is labeled, Preferred orientation angle. The left side of the base is labeled 180, the right side is labeled 0, and the top of the semicircle is labeled 90. The semicircle is divided into seven segments by straight lines originating from the center of the base. Each segment consists of a rectangle oriented such that the bottom end of the semicircle points toward the center of the semicircle.

Back to Figure

1. A black-and-white pixelated photo of Abraham Lincoln.
2. A black-and-white blurry photo of Abraham Lincoln.
3. A pixelated painting of the back of a nude woman looking at the Mediterranean Sea that has characteristics of the photo of Abraham Lincoln. Two of the pixels show a clearer picture of a woman looking at the sea and of Abraham Lincoln.

Back to Figure

The layers in the visual cortex, starting from the end of the occipital lobe, are V 1, V 2, and V 3. V 4 is on the ventral surface. V 5 or M T are two regions superior to V 3 on each hemisphere.

The dorsal stream of processing starts from V 1, passes through V 2, V 3, V 5 or M T, and posterior parietal complex, to the frontal lobe.

The ventral stream of processing starts from V 1, passes through V 4 and inferior temporal cortex, to the frontal lobe.

Back to Figure

1. The stimuli and their rankings are as follows:

    - Circle: 1
    - Upright rectangle: 1
    - Thin, upright rectangle: 1
    - A circle with spikes along the edge: 2
    - An upright rectangle with the top side replaced by a triangle: 3
    - A semicircle with spikes along the curved edge: 3
    - An inverted triangle with spikes along the base: 4
    - A closed fist: 4
    - A palm with five digits: 5

- A limb with four digits: 6

2. When a monkey’s face is unturned at 0 degrees, the response is high. As the monkey’s face turns by 30 degrees, 60 degrees, 80 degrees, 100 degrees, and 180 degrees, the level of response reduces. When the monkey’s face is unturned and the eyes are closed and for a human face, the level of response is approximately the same as when the monkey’s face is turned by 30 degrees.

Back to Figure

Greeble examples show a curved head without eyes and with beaks and a cap-like structure with protrusions on the head.

The f M R I scans of the ventral surface of the brain show that in greeble novice, there is high activation of fusiform gyrus in response to faces and no activation of the structure in response to greebles and in greeble expert, there is low activation of fusiform gyrus in response to faces and greebles.

Back to Figure

In the clock, the numbers on the left side of the face are on the center of the face, and the shape of the cock is slightly distorted.

In the house, the left side of the structure is missing, the right side is distorted, and the shape of doors and windows appear distorted.

Back to image

The ganglion cell is represented by a circle in the center, which is surrounded by a circular receptive field. The light is represented by a rectangle.

1. The rectangle of light covers on a small portion on the left side of the cell.
2. The rectangle of light covers the left side of the cell till the circle in the center.
3. The rectangle of light covers the left side of the cell and the circle in the center.
4. The rectangle of light covers the entire cell.

11 THE BODY SENSES AND MOVEMENT

Mads Perch/Stone/Getty Images

The Body Senses

- Proprioception
- The Skin Senses
- The Vestibular Sense
- The Somatosensory Cortex and the Posterior Parietal Cortex
- Pain and Its Disorders

A Further Look | Treating Pain in Limbs That Aren't There

Concept Check

Movement

- The Muscles
- The Spinal Cord
- The Brain and Movement

A Further Look | Brain-Computer Interfaces

Disorders of Movement

A Further Look | Deep Brain Stimulation and Parkinson's Disease

Concept Check

In Perspective

Chapter Summary

Study Resources

After reading this chapter, you will be able to

11.1 Identify the receptors involved in each type of skin sensation.

11.2 Describe the methods by which the brain gets information about the body and the environment.

11.3 Illustrate how the cortical areas for sensation correspond to portions of the body.

11.4 Assess the mechanisms by which pain is generated.

11.5 Summarize the brain structures involved in the production of movement.

11.6 Predict how movement is impaired in specific movement disorders.

One morning, Michael woke up with a strange sensation: His pinkie would not stop twitching. Stretching, even holding it straight, would stop the wiggle for a little while, but it would always start moving again uncontrollably after a minute or two. Over time, his twitching pinkie grew to a hand tremor, which eventually took over his arm. After seeing numerous physical therapists, doctors, and neurologists, he eventually received a diagnosis of this strange involuntary twitching: Parkinson's disease.

Michael was only 29, and Parkinson's disease is rare at such a young age. His doctors intimated that because of the progressive nature of the tremors, shuffling walk, and dyskinesia (uncontrollable movements), he had at most 10 more good working years as an actor before the symptoms would prevent him from acting again. As we'll see later, Michael's Parkinson's was a result of decreased dopamine levels, the neurotransmitter responsible for smooth movements. He was told that taking synthetic dopamine (L-dopa) would temporarily reduce, or even eliminate, the movement symptoms. Initially, he didn't tell anyone but his wife and threw himself into acting while he still was able to appear healthy to viewers. In the next few years, he played both major and minor roles in six films, recorded voices for seven animated films, and starred in a major television show called *Spin City*. Eventually, the tremors and movement problems became noticeable enough that he admitted he had the disease to the public (M. J. Fox, 2002).

After his diagnosis was made public. Michael could have simply asked for privacy and spent his time feeling sorry for himself. He did neither. Instead, he created one of the largest foundations dedicated to a cure for a single disorder—the Michael J. Fox Foundation for Parkinson's Research. In 1999, he testified in front of Congress

advocating for more federal funds dedicated to Parkinson's research (which typically receives a fraction of the funding that cancer and Alzheimer's disease receive), and he has fostered countless scientific advances through his foundation. But more than that, he has grown comfortable with his disorder, treating his symptoms with L-dopa only when *he* wants to, not just to look normal to others. As a result, he is not shy about showing the ravages of the disease on his own body, going off his L-dopa treatment in front of Congress to demonstrate how lack of dopamine changes your posture, movement, and speech while leaving your mind completely intact.

THE BODY SENSES

We get information about our body from the somatosensory system and from the vestibular system. The somatosenses include proprioception; the skin senses, which tell us about conditions at the surface of our body; and the interoceptive system, concerned with sensations in our internal organs. The vestibular system informs the brain about body position and movement. The interoceptive system operates mostly in the background and participates less directly in behavior, so we will limit our attention to the other systems.

Proprioception

Proprioception (from the Latin *proprius*, "belonging to one's self") is the sense that informs us about the position and movement of our limbs, body, and head. Its sensors report tension and length in muscles and the angle of the limbs at the joints. It also keeps track of our head as we move about the world. Proprioception is not as glamorous a sense as vision or audition, or even touch. However, without it, we would have a great deal of difficulty, like Michael J. Fox, in maintaining posture, moving our limbs, and grasping objects. This sense is what allows you to pick up your cell phone from where you put it down, without looking. Oliver Sacks (1990) tells the story of Christina, who lost all sense of proprioception following a bout with neuritis, an inflammation of the nerves that is often caused by a viral infection. Deprived of proprioceptive feedback, for the first month, she was floppy as a rag doll, unable even to sit upright. After a year of rehabilitation, she was able to resume a reasonably normal life, relying solely on vision to sit and stand erect and to walk. Ian Waterman, who is similarly afflicted, crumples helplessly onto the floor if someone turns the lights out (J. Cole, 1995). In other words, proprioception does more than provide information; it is critically important in the control of movement.

So what allows us to keep track of our body movements? Researchers have recently discovered the PIEZO2 receptor, which is embedded in the membranes of our muscles and body parts (Woo et al., 2015). Mutations in this receptor have been found in individuals with deficits similar to Christina's and Ian's (for example, Haliloglu et al., 2016).

? What is proprioception, and why is it important?

The Skin Senses

The commonly accepted **skin senses** are touch, warmth, cold, texture, and pain. However, three studies involving mice have found evidence that itch and tickle have their own receptors, neural pathway (spinothalamic tract), and receptor proteins (L. Han et al., 2012; Mishra & Hoon, 2013; Pandey et al., 2017); itch (which also goes by the interesting name of *pruriception*) will most likely be added to the list of skin senses. And there is evidence that tickle is processed by itch receptors as well. Whatever the actual number of skin senses, the important point here is that each is distinct from the others, with its own receptors and separate "labeled line" pathway to the brain. To demonstrate this for yourself, move the point of a lead pencil slowly across your face. You will feel the touch of the pencil continuously, but the lead will feel cold only occasionally—because touch and cold are monitored by different receptors. Although their range is limited to the surface of our body, changes there are often due to external stimulation, so the skin senses inform us about both our

body and the world. (We experience these sensations deeper in the body as well, but less often and with less sensitivity.) The skin sense receptors are illustrated in the diagram of a section of skin in Figure 11.1.

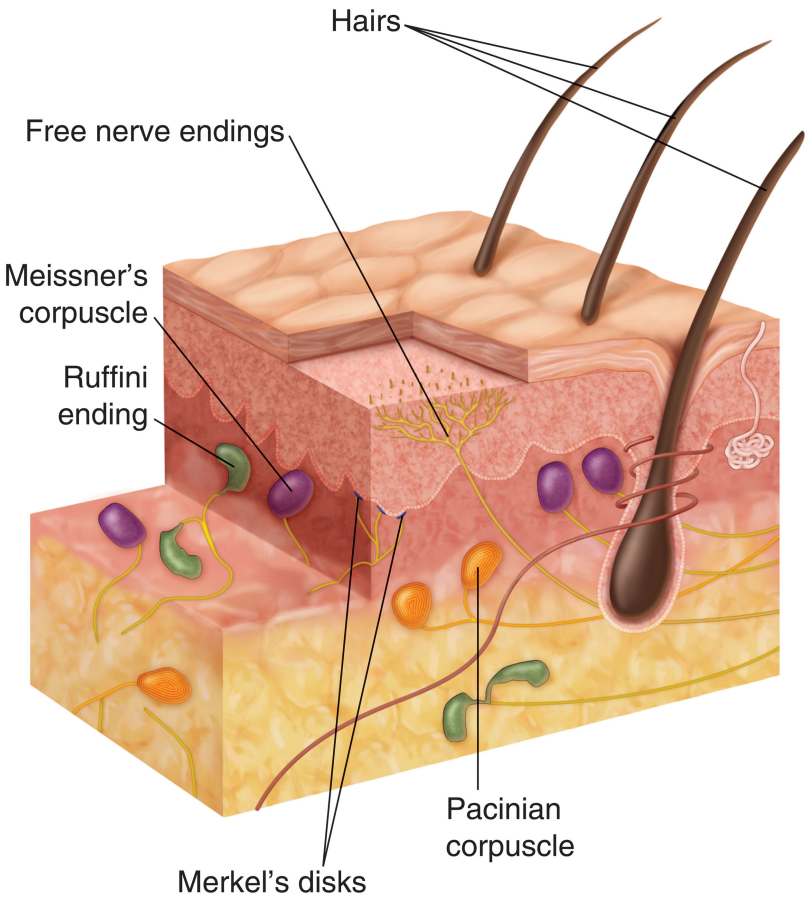


Figure 11.1 Receptors of the Skin.
The different endings of the receptors account for their varied specialties, which provide the brain with the rich information it needs to interact with the world.

? Why are there so many kinds of skin receptors?

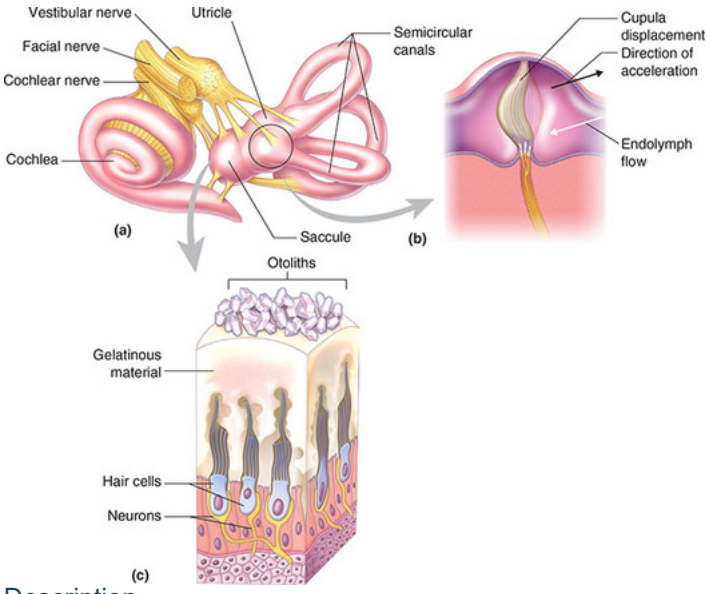
There are two general types of receptors. *Free nerve endings* are simply processes at the ends of neuronal dendrites; they detect warmth, cold, and pain. All the other receptors are *encapsulated receptors*, which are more complex structures enclosed in a membrane; their role is to detect touch. Why are there so many receptors just for touch? Because touch is a complex sense that conveys several types of information. In the superficial layers of the skin, Meissner's corpuscles respond with a brief burst of impulses, while Merkel's disks give a more sustained response. Located near the surface of the skin as they are, they detect the texture and fine detail of objects. They also detect movement and come into play when you explore an object with gentle strokes of your hand or when a blind person reads Braille. Pacinian corpuscles and Ruffini endings are in the deeper layers, where they detect stretching of the skin and contribute to our perception of the shape of grasped objects (E. P. Gardner & Johnson, 2013b). Because the density of the skin receptors varies throughout the body, so does sensitivity—as much as 10-fold, in fact. The fingertips and the lips are the most sensitive, and the upper arms and calves of the legs are the least sensitive (Weinstein, 1968).

The other three skin senses are detected by free nerve endings, but this statement is a bit misleading; those nerve endings have distinctly different receptors that make the

neurons stimulus specific (Basbaum, Bautista, Scherrer, & Julius, 2009). We can respond to a wide range of temperatures; at least two different receptors detect different levels of warmth, and another receptor responds to cooling of the skin. These receptors are all members of the *transient receptor potential (TRP)* family of protein ion channels. Detection of pain also requires several receptors, mostly because of the variety of pain sources; these sources are categorized as thermal, chemical, and mechanical. Two TRP receptors respond to painful heat; a receptor for painful cold has not been conclusively identified, but the coolness receptor does not account for this sensation. Chemical receptors react to a wide range of chemical irritants. Best known is the TRPV1 heat pain receptor, which also responds to capsaicin, the ingredient in chili peppers that makes spicy foods painfully hot. Ointments containing capsaicin alleviate the joint pain of arthritis, apparently because continued stimulation of the receptors depletes the neuropeptide that the neurons use to signal pain. This receptor also responds to the pain-inducing acid released in bone cancer, and a TRPV1 antagonist relieves this pain (Ghilardi et al., 2005). The TRPM8 coolness receptor produces the cool sensation of mint in toothpaste and candies, as well as the cooling effect of menthol and camphor on the skin; menthol and camphor creams are useful for treating muscle pain, skin irritations, and canker sores in the mouth. TRPA1 receptors are responsible for the painful irritation caused by vehicle exhaust, tobacco smoke, hydrogen peroxide, and tear gas, and they account for the pungency of mustard, garlic, and wasabi, as well as the tingle you get from a carbonated drink. As we will see shortly, the body produces its own irritants when tissues are damaged; these continue to produce pain well after the stimulus is past. The receptors for mechanical pain have not been determined, which is unfortunate because persistent hypersensitivity to touch is a major problem following tissue or nerve injury.

The Vestibular Sense

In Chapter 8, you saw that the cochlea in the ear is connected to a strange-looking appendage above it, the vestibular organ. The **vestibular sense** helps us maintain balance, and it provides information about head position and movement. Like the cochlea, the vestibular organ is filled with fluid. The organs include the three semicircular canals and the utricle and saccule (see Figure 11.2a). The physical arrangement of the semicircular canals, three loops arranged in different planes of orientation, makes them especially responsive to movement of the head in three directions. At the base of each canal is a gelatinous (jellylike) mass called a cupula, which has a tuft of hair cells protruding into it (Figure 11.2b). During acceleration (an increase in the rate of movement), the head (and the cupula) moves but the fluid does not, which causes the cupula to bend in the opposite direction of head movement proportionally to the rate of acceleration. This displacement bends the hairs attaching the cupula to the semicircular canal, which depolarizes them and increases the neuronal rate of firing. Moving the head in the opposite direction bends the hairs in the other direction, which hyperpolarizes the neuron and decreases the firing rate.



Description

Figure 11.2 The Vestibular Organs.
(a) The inner ear, showing the cochlea and the vestibular organs. (b) Enlarged view of a cupula in a semicircular canal. During acceleration, the flow of endolymph displaces the cupula, triggering a neural response. (c) Receptors of the utricle and saccule. Tilting the head causes the gelatinous material to shift, stimulating the hair cells. The weight of the otoliths (calcium carbonate crystals) magnifies the shift.

Sources: (a) Iurato (1967). (b) M. E. Goldberg, Walker, and Hudspeth (2013). © 2000 McGraw-Hill. (c) Based on Martini (1988).

? What are the types of information recorded by the vestibular sense?

The system responds only to acceleration and stops responding when speed stabilizes. Just as the coffee sloshes out of your cup when you start up from a traffic light and then levels off when you reach a stable speed, the fluid in the canals also returns to its normal position. Otherwise, you would continue to sense the movement throughout an automobile trip or, worse yet, during a 500-mile-per-hour (805-km/hr) flight in an aircraft!

The utricle and saccule monitor head position relative to gravity (detect where “up” is). In Figure 11.2c, you can see that the receptors (the hair cells) are covered with a gelatinous mass embedded with small calcium crystals called otoliths. When the head tilts, gravity shifts the mass and the hair cells are depolarized or hyperpolarized, depending on the direction of tilt. The hair cell receptors in the utricle are arranged in a horizontal patch, whereas the saccule’s receptors are on its vertical wall; together, the two organs can detect tilt in any direction.

Consider what would happen without a functioning vestibular system. Mr. MacGregor, one of Oliver Sacks’s patients, lost his vestibular sense to the neural degeneration of Parkinson’s disease (O. Sacks, 1990). When he walked, his body tilted to the left, a full 20 degrees. Strangely, Mr. MacGregor wasn’t aware of his tilt, even when his friends told him he was in danger of falling over. Once Sacks showed him a video of his movement, though, he was convinced. A retired carpenter, he put his expertise to work; 3 inches in front of his glasses he attached a miniature spirit level—a fluid-filled glass tube with a bubble in it that carpenters use to make sure their work is level with the world. By glancing at this makeshift device occasionally, he could walk without any slant, and after a few weeks, checking his tilt became so natural that he was no longer aware he was doing it.

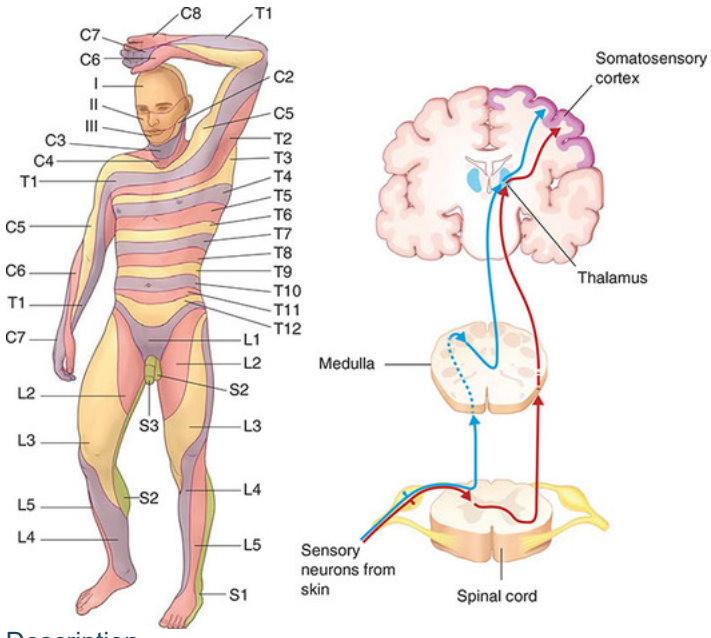
But the vestibular sense is not just for adjusting the body's position. When we reach for an object, we must know not just where the object is in three-dimensional space but also the position of our body and the relation of our hand and arm to our body. The brain combines information about the object's spatial location with inputs from the vestibular sense and from proprioception to tell us what arm and hand movements are required. Proprioception also triggers reflexive eye movements that keep focusing our gaze to a target object as we turn our head or as our body moves when we walk; otherwise, the world would become a meaningless blur and tracking moving objects would be very difficult. Movement encoded by the vestibular nerve is processed by the vestibular nuclei in the midbrain, which then sends information to the ocular nerves to produce compensatory eye movements. When people have balance problems, one of the first clinical signs is a failure of the person to fixate on an object when moving. You can see this for yourself: Spin a friend around in an office chair for 30 seconds; when the chair stops, you can see their eyes move repeatedly in the direction you spun them.

The semicircular canals and the utricle and saccule also send projections to the cerebellum and the brain stem, and there is also a pathway to the cortex, specifically to an area called the parieto-insular-vestibular (PIV) cortex. This is the likely location where excessive eye movements, from reading in a moving car, for example, cause dizziness and nausea. The PIV receives information from smell and taste receptors as well, which is why nausea and disgust are linked. The same thing happens with excessive body motion, for example, during a rough boat ride or from spinning around quickly. Doing the latter eventually causes the vestibular fluid to move with the head (like stirring a glass of water with a straw; at first the water resists movement, but eventually the water moves with the straw). When that happens and you stop, the fluid keeps moving, which makes the cupula continue to bend and makes you feel like you're spinning in the opposite direction. Figure skaters and gymnasts train themselves to focus on a single point when spinning and then turn their heads quickly to maintain that focus, which keeps the fluid from spinning. If you easily get motion or seasickness, chances are that you have a more sensitive PIV cortex. Taking an antihistamine drug (such as Dramamine) can decrease PIV activation and therefore reduce nausea.

? How are the body senses like other senses?

The Somatosensory Cortex and the Posterior Parietal Cortex

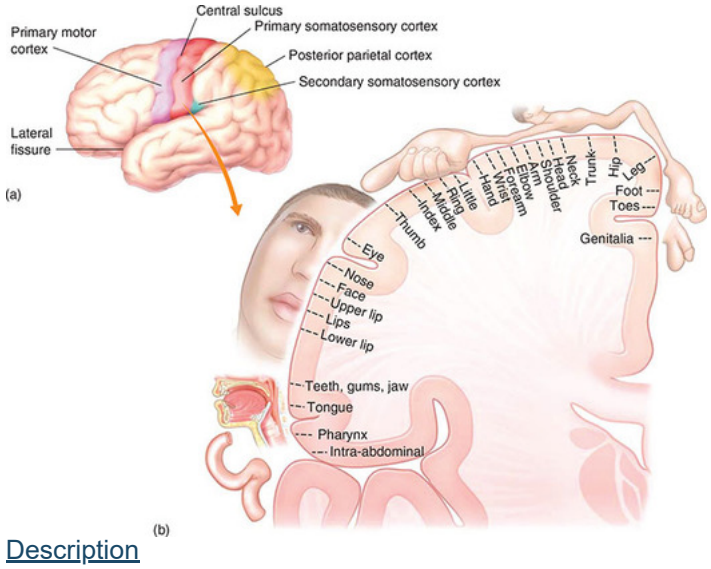
The body is divided into segments called **dermatomes**, each served by a spinal nerve, as Figure 11.3 shows. The divisions are not as distinct as illustrated, because each dermatome overlaps the next by one third to one half. This way, if one nerve is injured, the area will not lose all sensation. Body sense information enters the spinal cord (via spinal nerves) or the brain (via cranial nerves), crosses over the midline in the medulla, and travels to the thalamus. From there, the body sense neurons go to their projection area, the **somatosensory cortex**, located in the parietal lobes just behind the primary motor cortex and the central sulcus (Figure 11.4a). As with the auditory system, most of the neurons cross from one side of the body to the other side of the brain, so the touch of an object held in the right hand is registered mostly in the left hemisphere. Because not all neurons cross over, touching the object also stimulates the right somatosensory cortex, though much less.



Description

Figure 11.3 Dermatomes of the Human Body.
For sensory functions, the body is divided into segments called dermatomes, each served by a spinal or cranial nerve. The labels identify the nerve; letters indicate the part of the spinal cord where the nerve is located (cervical, thoracic, lumbar, or sacral), and the numbers indicate the nerve's position within that section. Areas I, II, and III on the face are innervated by branches of the trigeminal (fifth) cranial nerve.

Carolina Hrejsa/Body Scientific Intl.



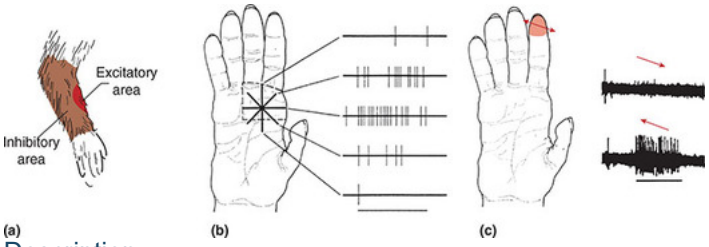
Description

Figure 11.4 The Primary and Secondary Somatosensory Areas.
(a) The primary and secondary somatosensory cortex and the posterior parietal cortex. The primary motor cortex is shown as a landmark. (b) A slice from the somatosensory cortex, showing its somatotopic organization. The size of the body parts in the figure is proportional to the area of the cortex in which they are represented. (The pictorial representation of the body on the cortex is called a *homunculus*.)

Source: Adapted from *The Cerebral Cortex of Man* by W. Penfield and T. Rasmussen, 1950, New York: Macmillan. © 1950 Gale, a part of Cengage Learning, Inc.

Carolina Hrejsa/Body Scientific Intl.

Sensory systems have many organizational and functional similarities; a comparison of the somatosensory cortex with the visual cortex will illustrate this point. First, it contains a **somatotopic map** of the body, with adjacent body parts represented in adjacent parts of the cortex, just as the visual cortex contains a map of the retina and the auditory cortex contains a map of the cochlea (Figure 11.4b). Second, some of the cortical cells have complex receptive fields on the skin. Some of them have excitatory center and inhibitory surround fields like those we saw in the visual system (Mountcastle & Powell, 1959). Some of them are quite large, as in Figure 11.5a, while smaller excitatory-inhibitory fields sharpen the localization of excitation and help distinguish two points touching the skin. In Figure 11.5b and 11.5c, we see that other somatosensory neurons with complex fields are feature detectors; they have sensitivities for orientation, direction of movement, shape, surface curvature, or texture (Carlson, 1981; E. P. Gardner & Johnson, 2013a; Warren, Hämäläinen, & Gardner, 1986). Apparently, these neurons combine inputs from neurons with simpler functions, just as complex visual cells integrate the inputs of multiple simple cells (Iwamura, Iriki, & Tanaka, 1994). One type of receptive field includes multiple fingers; the cells' firing rate depends on how many fingers are touched, so they give an indication of the size of a held object.



Description

Figure 11.5 Receptive Fields in the Monkey Somatosensory System.
(a) Excitatory and inhibitory areas of the receptive field of a single touch neuron in the somatosensory cortex. (b) Receptive field of a somatosensory neuron that responded most to a horizontal edge. The recordings to the right indicate the strength of the neuron's response to edges of different orientations. (c) Receptive field of a neuron responsive to movement across the fingertip in one direction but not the other.

Sources: (a) From "Neural Mechanisms Subserving Cutaneous Sensibility, With Special Reference to the Role of Afferent Inhibition in Sensory Perception and Discrimination," by V. B. Mountcastle and T. P. S. Powell, 1959, *Bulletin of the Johns Hopkins Hospital, 105,* p. 224, Figure 14. © The Johns Hopkins University Press. Reprinted with permission of the Johns Hopkins University Press. (b) and (c) From "Movement-Sensitive Cutaneous Receptive Fields in the Hand Area of the Post-central Gyrus in Monkeys," by J. Hyvärinen and A. Poranen, *Journal of Physiology, 283,* pp. 523–537. Copyright 1978, with permission from Elsevier.

A third similarity is that somatosensory processing is hierarchical. The *primary somatosensory cortex* consists of four areas, each of which contains a somatotopic map of the body and plays a role in processing sensory information from the body. The thalamus sends its output to two of these subareas, which extract some information and pass the result on to the other two areas, which in turn send their output to the secondary somatosensory cortex. At this point in processing, information from the right and left sides of the body is mostly segregated.

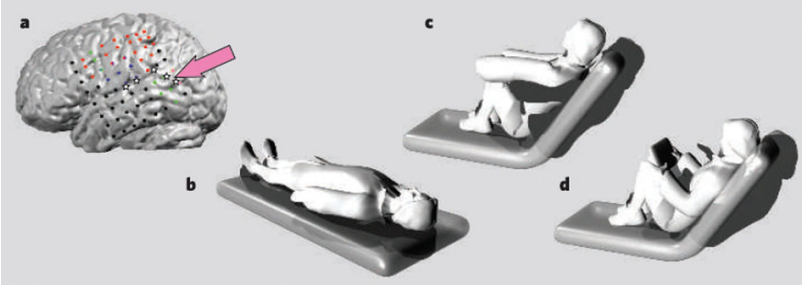
? What processing occurs at each level of the somatosensory system?

The **secondary somatosensory cortex** receives input from the left and the right primary somatosensory cortices, so it integrates information from both sides of the body. Neurons in this area are particularly responsive to stimuli that have acquired meaning, for instance, by association with reward (Hsiao, O'Shaughnessy, &

Johnson, 1993). The secondary somatosensory cortex sends connections to the part of the temporal lobe that includes the hippocampus. The hippocampus is important in learning, so these connections likely contribute to memory formation when somatosensory information is involved (E. P. Gardner & Johnson, 2013b).

The primary somatosensory cortex projects to the posterior parietal cortex as well as to the secondary somatosensory cortex. As you saw in Chapter 10, the **posterior parietal cortex** is an association area that brings together the body senses, vision, and audition (K. H. Britten, 2008). See Figure 11.4 again for the location of the posterior parietal cortex in relation to the somatosensory cortex. Here, the brain determines the body's orientation in space; the location of the limbs; and the location in space of objects detected by touch, sight, and sound. When you take a bite of apple pie, your posterior parietal cortex combines visual information about the forkful of pie with information about where your arm and hand are in relation to your body, how your head is oriented in relation to your body, and where your eyes are oriented in relation to your head. In other words, it integrates the body with the world. The posterior parietal cortex is composed of several subareas, which are responsive to different sense modalities and make different contributions to a person's interaction with the world. Some cells combine proprioception and vision to provide information about specific postures, for example, the location and positioning of the arm and the hand (Bonda, Petrides, Frey, & Evans, 1995; Graziano, Cooke, & Taylor, 2000; Sakata, Takaoka, Kawarasaki, & Shibutani, 1973). Others contribute to reaching and grasping movements and eye movements toward targets of interest (Batista, Buneo, Snyder, & Andersen, 1999; Colby & Goldberg, 1999). The posterior parietal cortex's contribution is not solely perceptual, because many of its neurons fire before and during a movement. It does not itself produce movements but passes its information on to frontal areas that do (Colby & Goldberg, 1999).

A unified body image is critical to our ability to function and even to our self-concept, so you can imagine that any disruption would have significant consequences. You saw in Chapter 10 that damage to the right posterior parietal cortex can produce neglect and that some stroke patients will deny ownership of a paralyzed arm or leg (called foreign limb syndrome or xenomelia). A few people with no apparent brain damage—or mental or emotional disorder, for that matter—are so convinced that a limb doesn't belong to them that they ask to have it amputated; this disorder is called **body integrity identity disorder**, or *apotemnophilia* (McGeoch et al., 2009). When the limb is touched, there is no response in the superior parietal area. Skin conductance response to stimulation is doubled in that limb, though, which indicates a high level of emotional feeling about the limb. A related phenomenon involving the same brain area incorporates the entire body into the illusion; in an **out-of-body experience**, the individual hallucinates seeing his or her body from another location, such as from a position above the body. Causes include traumatic brain damage and epilepsy affecting the junction between the parietal and temporal lobes; the experience can also be produced by electrical stimulation in that area (Blanke & Arzy, 2005). In a particularly spooky clinical example, a woman whose temporoparietal junction was stimulated to see if that was the source of her epileptic seizures reported a ghostly form right behind her that mimicked her body posture and movements precisely (Figure 11.6; Arzy, Seeck, Ortigue, Spinelli, & Blanke, 2006).



Description

Figure 11.6 Stimulating the Temporoparietal Junction Creates a Shadow "Person." The pink arrow and dots indicate the locations that elicited an imaginary second

person that mirrored the actions and positions of the patient. Other colored dots indicate associated functions (red was motor, green was language, and blue was somatosensory) and the trigger area for seizures (stars).

Source: From "Induction of an Illusory Shadow Person," by S. Arzy et al., *Nature, 443,* pp. 287, fig. 1.
© 2006. Reprinted by permission of Nature Communications.

Pain and Its Disorders

In Chapter 8, we learned about the emotional aspect of pain and how it motivates our behavior. Now we need to put pain in the context of the body senses and see how it works as a sensory mechanism. In spite of our attention to pain earlier, there are still a few surprises left.

Detecting Pain

Pain begins when certain free nerve endings are stimulated by intense pressure or temperature, by tissue damage, or by various chemicals. Tissue injury also causes cells to release a wide array of signaling molecules, referred to as the **inflammatory soup**; these include histamine, proteins (bradykinin and substance P), lipids (prostaglandins), neurotransmitters (serotonin), and cytokines (Julius & Basbaum, 2001; Kidd & Urban, 2001). Some of these stimulate pain receptors, but they also produce the familiar swelling and redness of inflammation, and they enhance excitability of the pain neurons so much that the neurons respond even to light touch. This effect is adaptive because it encourages guarding of the injured area, but the resulting pain can be more troublesome than the original injury. From the injured area, pain information travels to the spinal cord over large, myelinated A-delta fibers and small, lightly myelinated or unmyelinated C fibers. Because A-delta fibers transmit more rapidly than C fibers, you notice a *sharp, stinging pain* almost immediately when you are injured, followed by a longer-lasting *dull, aching pain* (Basbaum & Jessell, 2013). Sharp pain receptors tend to be superficially located and are much more densely packed, which makes localizing the source of the sharp pain easier. Dull pain receptors are deeper and respond to a wider array of painful stimuli, and the sensations are harder to localize (Raja, Meyer, Ringkamp, & Campbell, 1999). Sharp pain makes a good danger signal and motivates you to take quick action, while dull pain hangs around for a longer time to remind you that you have been injured.

? What causes pain?

In the spinal cord, pain neurons release the neurotransmitter glutamate; as stimulation becomes more intense, they release both glutamate and **substance P**, a neuropeptide that increases pain sensitivity (Chang & Leeman, 1970). In Chapter 2, we saw that neuropeptides enhance the primary neurotransmitter's effect at the synapse; in mice lacking substance P or its receptors, mild pain is unaffected but sensitivity to moderate and intense pain is impaired (Cao et al., 1998). As with the other body senses, pain information passes through the thalamus to the somatosensory cortex; however, the anterior cingulate cortex and the insula carry out additional processing of the emotional implications of pain, and the prefrontal cortex is concerned with pain of longer duration.

Treating Pain

We saw in Chapter 2 that local anesthetics—those that are applied to or injected into the painful area—block sodium channels in the pain neurons and reduce their ability to fire. General anesthetics, which may be injected or inhaled, render the patient unconscious. They work in the central nervous system, though their mechanism is poorly understood. We know that they affect the functioning of several proteins, but we don't know which ones are important to the anesthesia.

The most frequently used pain drugs are aspirin, ibuprofen, naproxen, and acetaminophen (Table 11.1). The first three (also called nonsteroidal anti-inflammatory drugs, or NSAIDs) block inflammatory enzymes required for producing prostaglandins, so they primarily reduce swelling and peripheral pain. Acetaminophen weakly blocks the same enzymes, so it has little anti-inflammatory benefit; its major effect is in the central nervous system. Ameliorating intense pain often requires more powerful substances called opiates (morphine extracted from the opium poppy is the acknowledged gold standard), but their addictiveness and patients' rapidly developing tolerance have spurred the development of numerous alternatives (refer to Chapter 5 for more on these drugs). The new MDAN series of drugs, for example, targets the mu opioid receptor while blocking the delta opioid receptor; these drugs are reportedly 50 times more potent than morphine, without producing either tolerance or addiction (Dietis et al., 2009). While promising, no mu opioid receptor drug has yet to make it to market; the promising drug oxycodegol (NKTR-0181) program was cancelled after a unanimous negative vote by the U.S. Food and Drug Administration (FDA), even after being fast tracked for testing and completing a successful Phase 3 clinical trial (Anson, 2020).

Table 11.1

TABLE 11.1 Currently Available Medications for Pain.

DRUG CLASS	EXAMPLES	METHOD OF ACTION	SIDE EFFECTS
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Naproxen, ibuprofen, aspirin	Decrease swelling in tissues	Increased risk of bleeding, stomach irritation, allergic reaction
COX-2 inhibitor (selective NSAID)	Celecoxib	Decreases inflammation	Slight risk of heart attack
Acetaminophen	Tylenol	Blocks pain signals in CNS	Liver problems
Opiates (narcotics)	Morphine, codeine, hydromorphone, oxycodone, fentanyl	Stimulate opiate receptors; block pain messages in CNS	Depressed breathing, sleepiness, addiction, tolerance, euphoria
Antidepressants	Serotonin-norepinephrine reuptake inhibitors (Cymbalta, Pristiq)	Increase available serotonin and norepinephrine circuits, decreasing physical and emotional pain	Sleepiness, weight gain, nausea

Efforts are underway on a variety of other fronts as well. Tanezumab, an antibody for nerve growth factor, has shown safety and effectiveness in clinical trials with chronic back pain and the inflammatory pain of joint arthritis (M. T. Brown et al., 2013; Cattaneo, 2010; B. Park, 2020). An experimental drug, NEO6860, that blocks the TRPV1 pain receptor produces modest reduction of knee pain in human participants (Arsenault et al., 2018). Some antidepressants (tricyclics and serotonin-norepinephrine reuptake inhibitors) also appear to be successful in alleviating chronic pain and pain that has an emotional component (D. M. Marks et al., 2009). In addition, cannabinoids appear to interact and suppress pain messages throughout the central nervous system (Bettinger & Chu, 2020). There has also been some preliminary success with gene therapy; patients whose pain from cancer was not relieved by 200 mg per day of morphine experienced an 80% reduction following treatment with a gene that increases endorphin production (D. J. Fink et al., 2011). The fact that pain ultimately occurs in the brain has inspired a novel approach that is also showing promise; chronic pain patients given continuous functional magnetic resonance imaging (fMRI) feedback of activity in their cingulate gyrus learned to reduce pain-related brain activity and their experience of pain (deCharms et al., 2005).

Internal Mechanisms of Pain Relief

People sometimes feel little or no pain in spite of serious injury; they may even fail to realize they are injured until someone calls it to their attention. In the account of his search for the mouth of the Nile River, the explorer and missionary David Livingstone (1858/1971) gave an intriguing example (Figure 11.7):

> Starting, and looking half round, I saw the lion just in the act of springing upon me. I was upon a little height; he caught my shoulder as he sprang,

and we both came to the ground below together. Growling horribly close to my ear, he shook me as a terrier dog does a rat. The shock produced a stupor similar to that which seems to be felt by a mouse after the first shake of the cat. It caused a sort of dreaminess, in which there was no sense of pain nor feeling of terror, though quite conscious of all that was happening. It was like what patients partially under the influence of chloroform describe, who see all the operation, but feel not the knife. (p. 12)

Figure 11.7 David Livingstone Attacked by a Lion.
Endorphins allowed him to endure the pain of a lion's attack.

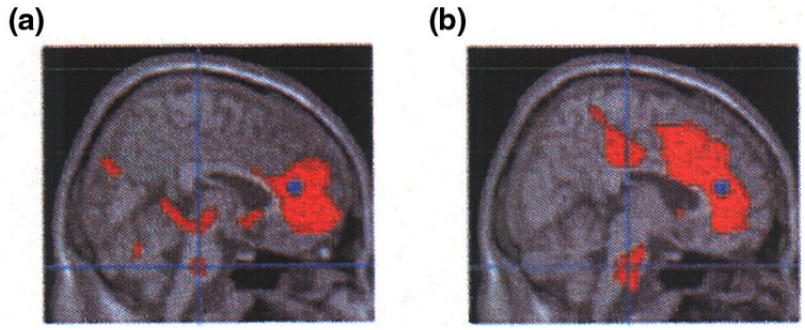
© iStockphoto.com/duncan1890

? How does the brain relieve pain?

You learned in earlier chapters that the reason opiate drugs are so effective at relieving pain is that they operate at receptors for the body's own pain relievers. Researchers combined the words *endogenous* ("from within") and *morphine* to come up with the name *endorphins* for this class of neurochemicals. *Endorphins* function both as neurotransmitters and as hormones, and they act at opiate receptors in many parts of the nervous system. Pain is one of the stimuli that release endorphins, but it does so only under certain conditions. Rats subjected to inescapable electric shock were highly tolerant of pain 30 minutes later; rats given an equal number of shocks that they could escape by making the correct response had only a slight increase in pain resistance (S. F. Maier, Drugan, & Grau, 1982). We are sure you can see the benefit of eliminating pain in situations of helplessness like Livingstone's and preserving pain when it can serve as the motivation to escape. An injection of naloxone eliminates the analgesia induced by inescapable shock but not the milder analgesia that follows escapable shock; the fact that naloxone blocks opiate receptors by occupying them indicates that the analgesia of inescapable shock is endorphin based. (You may be wondering how you would determine a rat's pain resistance, given that it cannot verbally report its pain sensation. One way is to place the rat's tail under a heat lamp and record how long it takes the rat to flick its tail away.)

Several kinds of stimulation result in endorphin release and pain reduction, including physical stress (Colt, Wardlaw, & Frantz, 1981), acupuncture (Watkins & Mayer, 1982), eating sugary foods (D. T. Fullerton, Getto, Swift, & Carlson, 1985), and sexual stimulation in female rats (Komisaruk & Steinman, 1987) and women (Whipple & Komisaruk, 1988). Analgesia resulting from sexual stimulation probably serves to reduce pain during birth or intercourse. Even the pain relief from placebo, which doctors once took as evidence that the pain was not "real," is often the result of

increasing endorphins, as revealed both by naloxone blockage of opiate receptors and by PET scans (Figure 11.8; Amanzio, Pollo, Maggi, & Benedetti, 2001; Petrovic, 2005; Petrovic, Kalso, Petersson, & Ingvar, 2002). So convincing yourself that the pain is diminishing may actually decrease the pain!



Description

Figure 11.8 Activation of Opiate Receptors in the Brain by a Placebo.
(a) Activity in cortical and brain stem areas (in red) during opiate drug treatment for pain. (b) A similar pattern of activity occurs during placebo treatment of pain. Pain alone did not produce this result. The blue dots indicate the location of the anterior cingulate cortex, which, as you saw in Chapter 8, is involved in emotional aspects of pain.

Source: From "Placebo and Opioid Analgesia—Imaging a Shared Neuronal Network," by P. Petrovic et al., *Science, 295,* pp. 1737–1740, fig. 4 a and b, p. 1739. © 2004. Reprinted by permission of AAAS.

Not all stimulation-induced pain relief comes from endorphins. For example, naloxone does not reduce the analgesic effect of hypnosis, and naloxone blocks analgesia produced by acupuncture needles inserted at distant points from the pain site but not when the needles are placed near the site (Watkins & Mayer, 1982). Research indicates that the acupuncture needle causes a 24-fold increase in adenosine, which acts as a local anesthetic (Goldman et al., 2010). (Note, by the way, that this study's first author was a 16-year-old girl.)

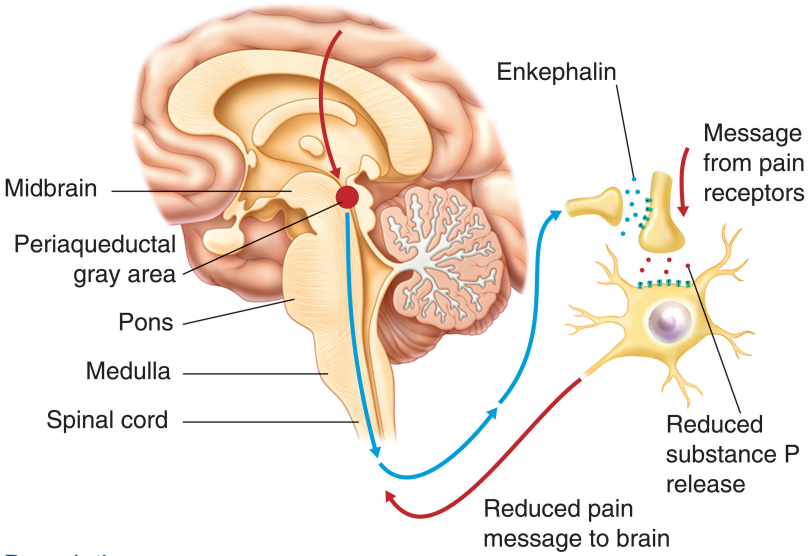
The Descending Pain Inhibition Circuit

During a spring break in New Orleans, Bob was touring one of the Civil War–era plantation houses for which the area is noted. In a glass case was an assortment of artifacts that had been found on the plantation grounds. An odd part of the collection was a few lead rifle slugs with what were obviously deep tooth marks on them. When makeshift surgery had to be performed with only a large dose of whiskey for anesthesia, the unfortunate patient would often be given something to bite down on, such as a piece of leather harness or a relatively soft lead bullet. (You can probably guess the common expression that is associated with this practice.) As a toddler, when you scraped your knee, you clenched your teeth and rubbed the area around the wound. And—tribute to your childhood wisdom—it really did help and got you through the pain without the benefit of either a lead bullet or whiskey. You might think that tooth clenching and rubbing simply take attention from the pain. Ronald Melzack and Patrick Wall (1965) had another idea. In their **gate control theory**, they hypothesized that pressure signals arriving in the brain trigger an inhibitory message that travels back down the spinal cord, where it closes a neural "gate" in the pain pathway.

? How can we "gate" pain?

Research has confirmed the general idea of their theory, and we now know that a descending pathway in the spinal cord is one of the ways the brain uses endorphins to control pain. Pain causes the release of endorphins in the **periaqueductal gray (PAG)**, a brain stem structure surrounding the cerebral ventricles with a large number

of endorphin synapses (Basbaum & Fields, 1984). As you can see in Figure 11.9, endorphin release inhibits the release of substance P, closing the pain "gate" in the spinal cord. (Note that enkephalin, the type of endorphin in the spinal cord, reduces substance P release by *presynaptic* inhibition, as described in Chapter 2.) Activation of the endorphin circuit apparently has multiple neural origins, including the cingulate cortex during placebo analgesia and the amygdala in the case of fear-induced analgesia (Petrovic, 2005). Brain imaging shows that placebo reduces pain through this circuit, and so does simple distraction (Petrovic, 2005; Petrovic et al., 2002; Tracey et al., 2002). Electrical stimulation of the PAG is also a very effective pain reliever, but it has the drawback of implanting electrodes in the brain (Bittar et al., 2005). Women, unfortunately, have fewer mu opioid receptors in the PAG than men, so they receive less pain-relieving benefit from opiate drugs (Loyd, Wang, & Murphy, 2008). The PAG also contains cannabinoid receptors, which respond to endogenous cannabinoids and the active ingredient in marijuana (see Chapter 5), and they account for some forms of stimulation-induced pain relief (Bettinger & Chu, 2020; Hohmann et al., 2005).



Description

Figure 11.9 The Descending Pain Inhibition Circuit.
Endorphin release in the periaqueductal gray inhibits the release of substance P by pain neurons in the spinal cord; this reduces the pain message reaching the brain.

Pain's Extremes: From Congenital Insensitivity to Chronic Pain

Congenital insensitivity to pain (or congenital analgesia) is a very rare condition. This is fortunate, because those who are afflicted not only unknowingly hurt themselves but also often engage in risky and dangerous behavior that most other people avoid. One family with several afflicted members was discovered when researchers learned of a boy in northern Pakistan who entertained on the street by piercing his arms with knives; before he could be studied, he died when he celebrated his 14th birthday by jumping off a roof (J. J. Cox et al., 2006). Several genes have been identified as responsible for the different kinds of pain insensitivity. People with an autosomal recessive mutation in the *SCN9A* gene have nonfunctioning versions of a specific sodium channel, so their pain neurons are disabled (J. J. Cox et al., 2006). Mutations in the *PRDM12* gene also prevent the development of pain-sensing neurons (Y.-C. Chen et al., 2015). Those with a mutation in the gene for nerve growth factor (*NGFB*), which stimulates development of sensory nerves, have a significant loss of unmyelinated neurons and less severe loss of myelinated fibers (Einarsdottir et al., 2004). Another cause of insensitivity is illustrated in the case of a 16-year-old boy

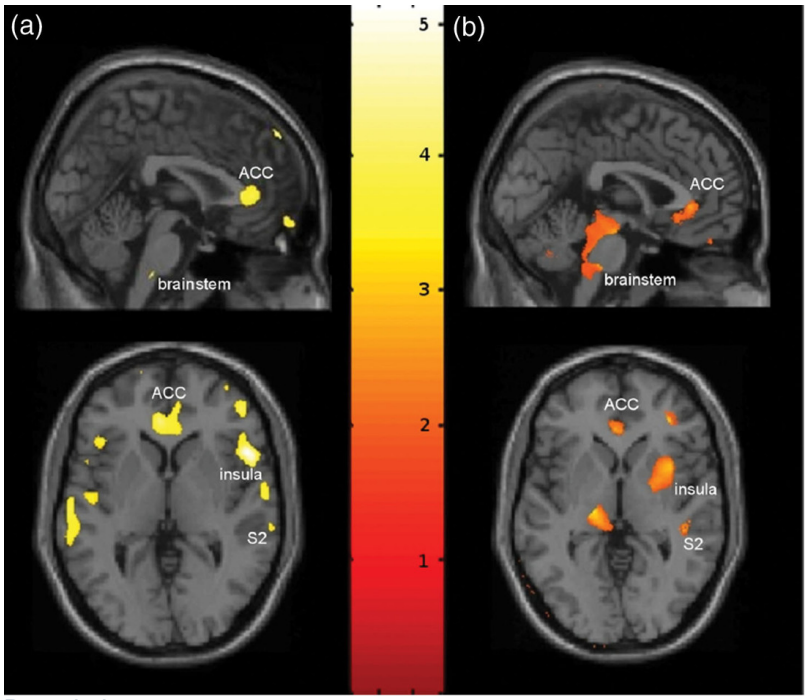
whose most significant characteristic was naturally elevated opioid levels in his cerebrospinal fluid (Manfredi et al., 1981).

? How does chronic pain differ from regular pain?

Chronic pain is much more common, and its victims often experience lifelong suffering. How many people are afflicted is difficult to determine, because studies include different populations and use different criteria. In 2016, the National Health Interview Survey found that 20% of U.S. adults suffer from chronic pain, and 8% are so affected by pain that it interferes with their daily lives (Dahlhamer et al., 2016). Practitioners often attempt to distinguish chronic from acute pain in terms of duration, with standards varying from 1 month to 1 year. However, it makes more sense to define **chronic pain** as pain that persists after healing has occurred or beyond the time in which healing would be expected to occur.

Whether pain becomes chronic is largely unrelated to the severity of injury. Chronic pain patients are often clinically depressed; this could logically be attributed to the pain, but evidence indicates that in patients who exaggerate the extent and intensity of their pain, the depression precedes the injury (Bortsov, Platts-Mills et al., 2013). Also, the strength of functional connectivity between the nucleus accumbens and the frontal cortex, measured shortly after back pain began, predicted with 85% accuracy which patients would continue to suffer pain 1 year later (Baliki et al., 2012). Both areas are important in evaluating and dealing with stressful events, and their connection likely determines how emotionally the person reacts to pain. Several genes play a role as well. A different allele of the *SCN9A* sodium channel gene mentioned earlier lowers pain thresholds and contributes to two types of neuropathic pain (Fischer & Waxman, 2010). Variations in the *COMT* gene (which inactivates neurotransmitters in the synapse) also regulate pain sensitivity, as well as responsiveness to pain relievers, and they figure in several pain syndromes (Andersen & Skorpen, 2009). Six variations of a glucocorticoid gene were associated with increased pain intensity in patients following motor vehicle collisions, while a variant of a D_2 dopamine receptor gene reduced severity (Bortsov, Smith, et al., 2013; Qadri et al., 2012).

The nervous system undergoes extensive functional and structural changes during chronic pain. The pain pathways increase their sensitivity, new connections sprout where peripheral neurons make connections in the spinal cord, and normal spinal inhibitory mechanisms are depressed (Woolf & Salter, 2000). The brain also participates in these changes. Brain stem pathways become more responsive (M. Lee, Zambreanu, Menon, & Tracey, 2008); activation increases in the prefrontal cortex, anterior cingulate cortex, and insula (Baliki et al., 2006); and the amount of somatosensory cortex devoted to the painful area expands (Flor, Braun, Elbert, & Birbaumer, 1997). There is considerable loss of gray matter, equivalent to 10 to 20 years of additional aging in patients with chronic back pain (Figure 11.10; Rodriguez-Raecke, Niemeier, Ihle, Ruether, & May, 2009) and 9.5 years of additional aging per year of suffering with fibromyalgia (Kuchinad et al., 2007). Evidence of the functional disruption this causes is that chronic pain patients perform poorly, almost randomly, on the gambling test used to assess prefrontal impairment (described in Chapter 8; Apkarian et al., 2004). One piece of good news is that cortical decline may be partially reversible; patients with chronic hip pain increased their gray matter volumes after receiving a hip replacement and going 4 months without pain (Rodriguez-Raecke et al., 2009).



Description

Figure 11.10 Gray Matter Loss, Then Gain, in Patients With Chronic Hip Pain Before and After Replacement Surgery.
Magnetic resonance imaging shows areas where patients lost more gray matter than controls in the anterior cingulate cortex, insula, and brain stem. (a) Yellow represents the amount of loss in chronic pain patients compared to pain-free controls, and (b) orange represents postsurgical gain compared to presurgical size in patients with chronic hip pain.

Source: From "Brain Gray Matter Decrease in Chronic Pain Is the Consequence and Not the Cause of Pain," by Rodriguez-Raecke et al., *Journal of Neuroscience, 29,* pp. 13746–13750, fig. 1. © 2009 Society for Neuroscience. Used with permission.

Phantom Pain

If damage to the right parietal cortex can eliminate recognition of a paralyzed left arm or leg, shouldn't removing a person's arm or leg eliminate all consciousness of the limb? Not if there are cortical areas still devoted to the missing body parts. Most amputees continue to experience the missing limb, not as a memory but as vividly as if it were real (Melzack, 1992). A phantom leg seems to bend when the person sits down and then to become upright during standing; a phantom arm even feels as though it is swinging in coordination with the other arm during walking.

? What causes phantom pain?

In about 75% of amputees, we see what is undeniably the strangest manifestation of chronic pain (Kern, Busch, Rockland, Kohl, & Birklein, 2009; Richardson, Glenn, Nurmikko, & Horgan, 2006). **Phantom pain**, pain that is experienced in a missing limb, is not simply pain at the stump but is felt in the missing arm or leg itself. The classical explanation was that the cut ends of nerves continue to send impulses to the part of the brain that once served the missing limb. Peripheral input is a factor in some cases, but anesthetizing these nerves relieves phantom pain in no more than half of patients (Birbaumer et al., 1997; Flor, 2008), so something else must be going on.

Following the clue that stimulating the face often produces sensations in a phantom arm, a team of researchers in Germany used brain imaging to map face and hand somatosensory areas in upper-limb amputees (Flor, 2008). In patients with phantom pain, neurons from the face area appeared to have invaded the area that normally receives input from the missing hand (Figure 11.11). The area activated by touch on the lips was shifted an average of 2.05 centimeters (cm) in the hemisphere opposite the amputation, compared with 0.43 cm for the patients without phantom pain, a five-fold difference. It is unclear how much the results were due to intrusion of foreign neurons or to activation of existing neurons. However, facial stimulation can evoke sensations in the phantom arm within 24 hours after amputation, which indicates that "unmasking" of existing but ordinarily silent inputs is at least a partial explanation (Borsook et al., 1998). We usually think of neural plasticity as adaptive, but sometimes it can lead to malfunction and, in this case, truly bizarre results. As you can imagine, treating phantom pain poses special problems, so we will give it special attention in A Further Look.

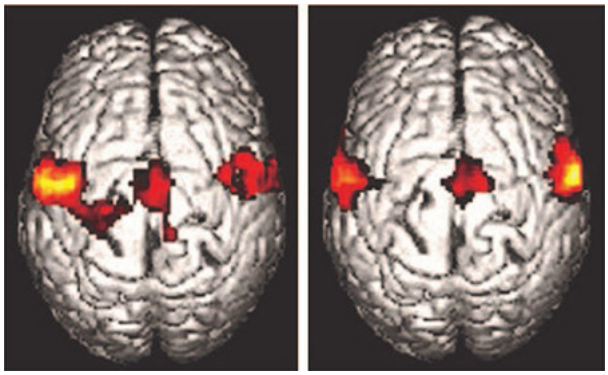


Figure 11.11 Reorganization of the Somatosensory Cortex in a Phantom Pain Patient Following Arm Amputation.
Patients were asked to pucker their lips rhythmically while being scanned in an fMRI machine. On the left, individuals reporting phantom pain had their right ventral mouth area invading the dorsal hand area. On the right, individuals without phantom pain did not show any changes. See Figure 11.4 for the homunculus map of these areas.

Source: From "Maladaptive Plasticity, Memory for Pain and Phantom Limb Pain: Review and Suggestions for New Therapies," by H. Flor, 2008, *Expert Reviews in Neurotherapeutics, 8,* pp. 809–818. Copyright © 2008.

A Further Look:

Treating Pain in Limbs That Aren't There

Source: © Walter Morris/Medill News Service.

Most treatments for phantom pain are ineffective and fail to consider the mechanisms producing the pain. Surgery and pharmacological interventions are typically no better than placebo and benefit less than 30% of patients (Flor, 2008). Postsurgical reorganization of cortical wiring is a likely cause of phantom limb pain (Yanagisawa et al., 2016). The stochastic entanglement hypothesis, for example, proposes that this occurs when random firing in the unused neurons in the somatosensory area that previously served the missing limb coincides with firing in the pain neurons that are active following amputation, causing them to “wire together” (Ortiz-Catalan, 2018). Several studies suggest that therapies that work either prevent or reverse the cortical reorganization that occurs following amputation (Birbaumer et al., 1997). Use of a functional prosthesis (as opposed to a purely cosmetic one) prevents cortical reorganization and reduces pain occurrence (Lotze et al., 1999); newer hand prostheses that have pressure sensors in the fingers to help amputees adjust their grip to different objects should reduce phantom pain even better (Friedrich-Schiller-Universität Jena, 2010). When a prosthesis is impractical, training to discriminate electrical stimuli applied to the stump reverses cortical reorganization and reduces pain in 60% of patients (Flor, Denke, Schaefer, & Grüsser, 2001).

One promising behavioral technique is mirror therapy. The patient places the stump out of sight on one side of a mirror and the good limb on the other side, so the reflection of the good limb appears to replace the one that is missing (see figure). Then the patient is told to move the two limbs in unison. In one later study, 100% of patients using the mirror box experienced decreases in pain (Chan et al., 2007); another study confirmed that pain relief is accompanied by reversal of cortical reorganization (Flor, Diers, Christmann, & Koeppe, 2006). For obvious reasons, mirror therapy is most effective if it is used soon after injury (Foeli, Bekrater-Bodmann, Diers, & Flor, 2013), but an augmented reality technique is proving effective in patients more than 5 years after their amputation and previous treatment (Ortiz-Catalan et al., 2016). Instead of a mirror image, patients see themselves on a video screen with their amputated arm replaced by a virtual one; electrodes on the stump send electrical signals from the muscles to a computer to make the virtual arm move. After 12 sessions, the patients’ pain decreased by 50%.

These techniques may work because of the greater responsiveness of the mirror neuron system in phantom limb patients. Bob saw this firsthand in a colleague, Ed, who had lost both legs in an accident. As they watched a construction worker walking the girders of a new building, Bob felt a bit of anxiety and a sympathetic tension in his legs as he imagined himself up there balancing on the narrow beams, but to his surprise, Ed exclaimed, “That makes my ankles hurt!” Researchers believe that

simulated feedback therapy works because the image triggers exaggerated activity in mirror neurons in the hemisphere that once served the missing limb (Chan et al., 2007; Ramachandran & Altschuler, 2009). Without contradictory feedback from the missing limb, the mirror neuron activity is interpreted as actual touch or movement, and with continued practice, the brain's reorganization is reversed.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- What is the contribution of each of the three classes of body senses?
- In what ways are the somatosensory cortex and the visual cortex organized similarly?
- In what circumstances does the brain reduce pain?

MOVEMENT

A popular view of the brain is that it is mostly preoccupied with higher cognitive processes, such as thinking, learning, and language. However, a surprising proportion of the brain is devoted to planning and executing movements. We are talking about more than simply moving the body from one place to another; consider the surgeon's coordinated hand movements during a delicate operation, the control of mouth and throat muscles and diaphragm required to sing an aria, or a baseball outfielder's ability to track a fast-moving fly ball and arrive in time to catch it. Studies of the control of movement provided one of the earliest windows into the brain's organization and functioning, and it is that facet of the research that will interest us most. Before we launch into that topic, we need some understanding of the equipment the brain has to work with.

The Muscles

We have three types of muscles. The ones you are most familiar with are the **skeletal muscles**, which move the body and limbs but can fatigue if overused; they are also called *striated* muscles because of their striped cellular appearance. **Smooth muscles** produce rhythmic contractions in the internal organs; for example, they move food through the digestive system, constrict blood vessels, and void the bladder. **Cardiac muscles** are the non-fatiguing muscles that make up the heart. Because our focus is on movement, we will concentrate on the skeletal muscles. But despite differences in appearance, the muscles function similarly.

Like other tissues of the body, a muscle is made up of many individual cells, or muscle fibers. The muscle cells are controlled by motor neurons that synapse with a muscle cell at the neuromuscular junction using the neurotransmitter acetylcholine (Figure 11.12). The number of cells served by a single axon determines the precision of movement possible. The biceps muscles have about 100 muscle fibers per axon, but the ratio is around 3 to 1 in the eye muscles, which must make very precise movements in tracking objects (Evarts, 1979).

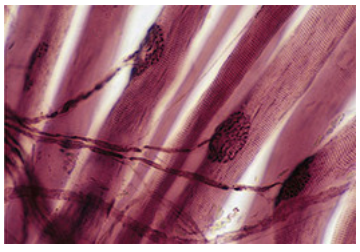


Figure 11.12 Muscle Fibers Innervated by a Motor Neuron.

Source: © Ed Reschke/Photolibrary/Getty Images.

A muscle fiber is made up of myosin and actin filaments. When a motor neuron releases acetylcholine, the muscle fiber is depolarized, which opens calcium channels; the calcium influx initiates a series of actions by the myosin that contract the muscle. The heads of the myosin filaments attach to the surrounding actin filaments; the myosin filaments then contract the heads to pull on the actin filaments. This makes a stroking movement that causes the actin filaments to slide along the myosin filaments, shortening the muscle fibers. The heads then release and reattach higher up on the actin filaments. (Think of using your fingertips to rapidly pull a piece of paper toward you on your desk.) This sequence repeats rapidly, contracting the muscle (Figure 11.13).

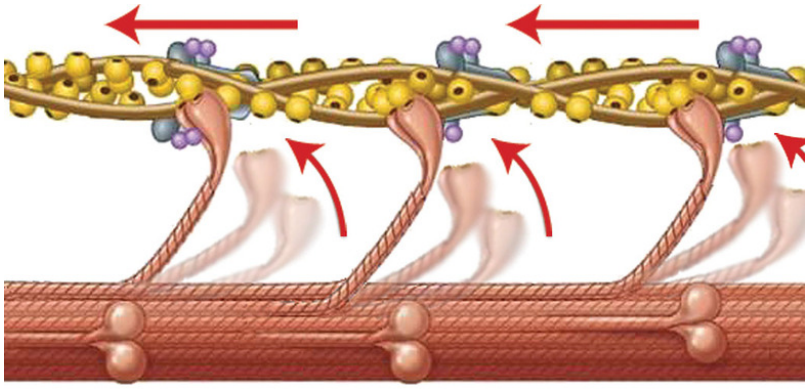


Figure 11.13 Myosin and Actin Cause a Muscle to Contract.
Protrusions from the myosin filament extend to the actin filament and attach, then flex, causing the actin to slide alongside the myosin; this shortens the muscle, producing a contraction. The protrusions then withdraw from the actin and repeat the process in rapid succession.

Source: Adapted from Figure 10.7, *Principles of Anatomy and Physiology* (11th ed.), by Gerard J. Tortora and Bryan H. Derrickson, 2006, Hoboken, NJ: John Wiley & Sons.

Skeletal muscles are anchored to bones across a joint by tendons, which are tough fibrous bands of connective tissue. You can see in Figure 11.14 that the muscles are able to operate the limbs like levers to produce movement by pulling against their attachments. Muscles can only contract; a limb is both flexed and extended by pulling on the joint from one side or the other. You can see that limbs have **antagonistic muscles** that produce opposite movements at a joint. In this case, the biceps muscle decreases the arm angle to flex the arm, and the triceps increases the angle, extending the arm. Rather than one muscle relaxing while the other does all the work, movement involves opposing contraction from both muscles. The simultaneous contraction of antagonistic muscles creates a smoother movement, allows precise stopping, and maintains the limb angle with minimal tremor. Standing requires complex coordination of antagonistic muscles in the legs as well as muscles in the torso. The strength and duration of muscle contraction varies from moment to moment, so the balance between antagonistic muscles is constantly shifting, constantly correcting. If maintaining the balance between opposed pairs of muscles required conscious, voluntary activity, we would find it very difficult to hold a camera still enough to get a sharp picture or even to stand or sit erect. Adjustments this fast must be controlled by reflexes at the level of the spinal cord.

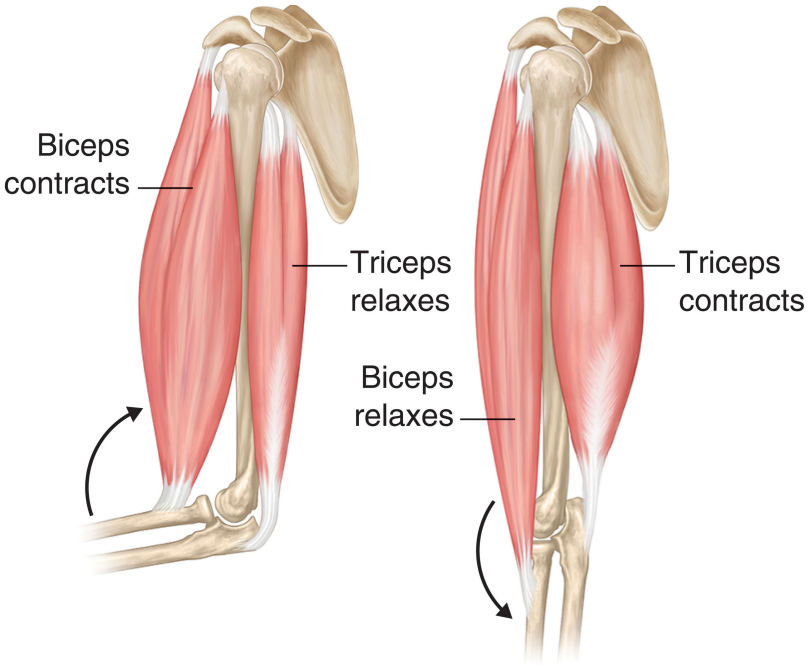


Figure 11.14 Antagonistic Muscles of the Upper Arm.
When the biceps muscle contracts, it flexes the arm (left); contracting the triceps muscle extends the arm.

Source: Based on Starr and Taggart (1989).

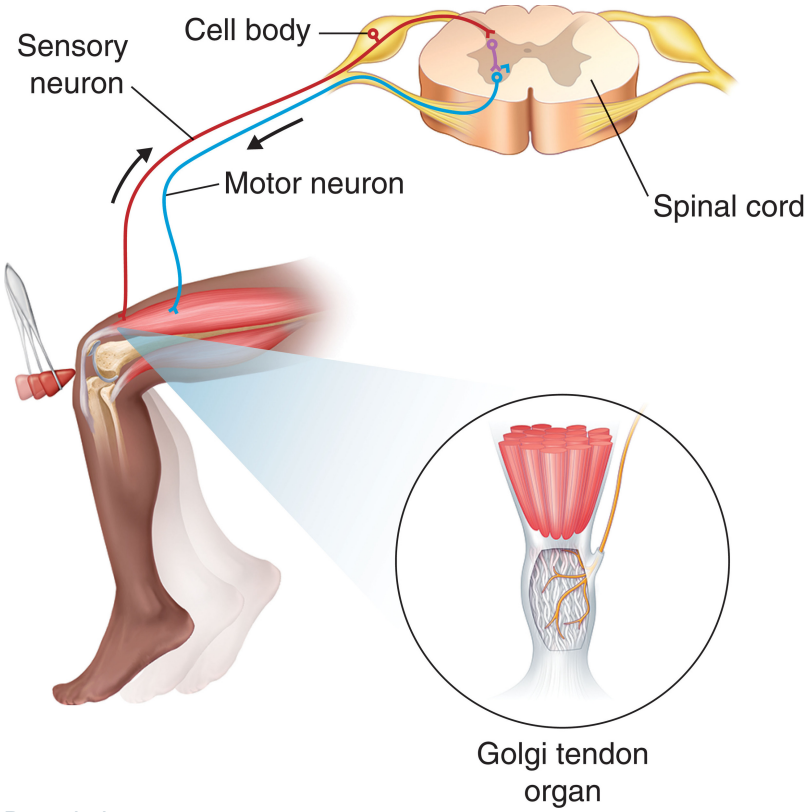
? What is the function of antagonistic muscles?

The Spinal Cord

In Chapter 3, we introduced the idea of the spinal reflex. Everyone is familiar with the reflex that makes you quickly withdraw your hand from a hot stove. When you step on a sharp object, you reflexively withdraw your foot and simultaneously make a variety of reflexive postural adjustments to avoid losing your balance. The advantage of reflexes is that we can make the appropriate adjustments quickly, without the delay of having to figure out the right action.

? What do spinal reflexes and central pattern generators do?

The monosynaptic reflex illustrated in Figure 11.15 should also be familiar. Your doctor taps the patellar tendon, which connects the quadriceps muscle to the lower leg bone. This stretches the muscle, which is detected by muscle stretch receptors called **muscle spindles** and relayed to the spinal cord. There the sensory neurons synapse on motor neurons, which return to the quadriceps and cause it to contract and extend the lower leg. (There is an inhibitory interneuron in the spinal cord that relaxes the antagonistic hamstring muscle in the back of the leg, but this isn't shown in the figure.) The function of the stretch reflex is not just to amuse your doctor. It enables a muscle to resist very quickly if the muscle is stretched by activity in its antagonistic partner; this helps, for example, to maintain an upright posture. It also allows a muscle to respond quickly to an increased external load, for example, when you are holding a stack of books in front of you and a friend unexpectedly drops another book on top of it. **Golgi tendon organs**, receptors that detect tension in a muscle, trigger a spinal reflex that inhibits the motor neurons and limits the contraction. This prevents muscles from contracting so strongly that they might be damaged.



Description

Figure 11.15 The Patellar Tendon Reflex, an Example of a Stretch Reflex. The hammer stretches the tendon, causing a reflexive contraction of the extensor muscle and a kicking motion. This is a highly simplified representation; many more neurons are involved.

More complex patterns of motor behavior are also controlled in the spinal cord. It has been known for at least a century that cats with severed spinal cords, eliminating control from the brain, can make rhythmic stepping movements and walk when they are suspended with their feet on a treadmill (J. G. Jones, Tansey, & Stuart, 2011). This behavior depends on **central pattern generators (CPGs)**, neuronal networks that produce a rhythmic pattern of motor activity, such as those involved in walking, swimming, flying, and breathing. CPGs are in the spinal cord and in the brain and have been found in all vertebrate and in many invertebrate animals. In humans, they are most obvious in infants below the age of 1 year, who can make stepping movements when held with their feet on a treadmill (Lamb & Yang, 2000). In adults, CPGs provide an important bit of automaticity to routine movements. They can be elicited in individuals with spinal cord injury to produce rhythmic stepping movements (Dimitrijevic, Gerasimenko, & Pinter, 1998), and researchers are working on ways to recruit them during therapy (Boulenguez & Vinay, 2009; Dietz, 2009; Edgerton & Roy, 2009). Spinal reflexes produce quick, reliable responses, and CPGs provide basic routines the brain can call up when needed, freeing the brain for more important matters (Figure 11.16). But reflexes and CPGs cannot provide all our movement capabilities, so we will turn our attention to the contributions the brain makes to movement.

Figure 11.16 The Stepping Reflex.
The stepping reflex is present in young infants. If you support their weight and allow their feet to touch a flat surface, they will raise and lower their legs as though they are walking.

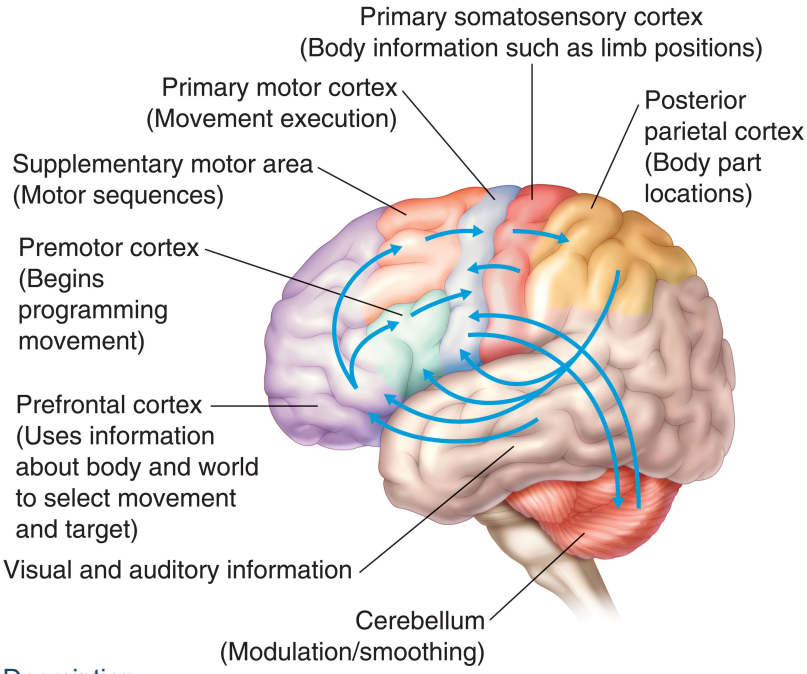
Source: © Phanie/Phanie/SuperStock.

The Brain and Movement

In the motor system, we again see a hierarchical organization consisting of the forebrain, brain stem, and spinal cord. The motor cortex organizes complex acts and executes movements while modulating activity in the brain stem and spinal cord. The brain stem in turn modulates the activity of the spinal cord (Wolpert, Pearson, & Ghez, 2013). We will start with the cortex and give it most of our attention.

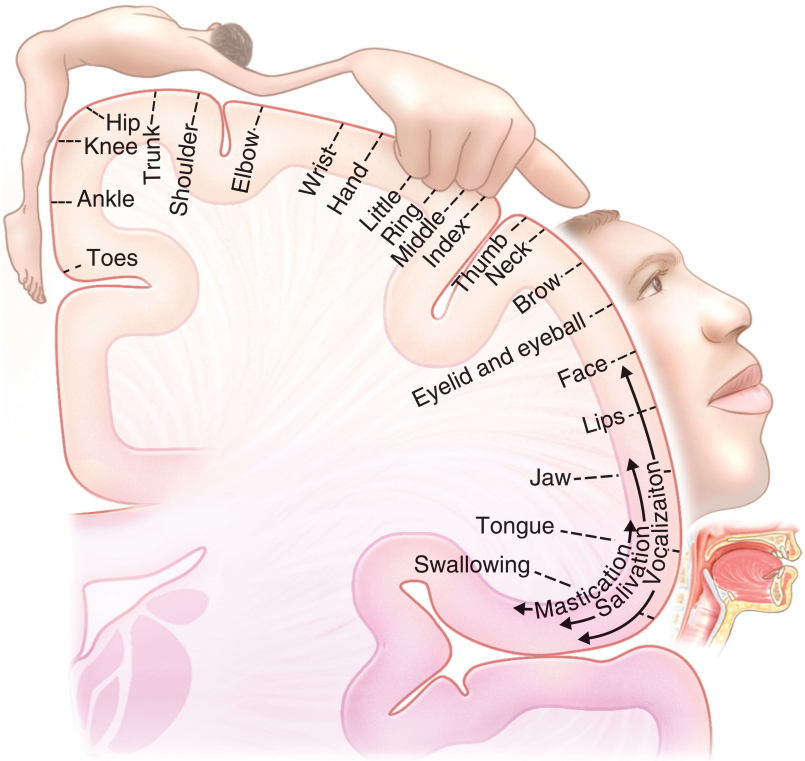
The motor cortex consists of the *primary motor cortex* and two major secondary motor areas, the *supplementary motor area* and the *premotor cortex* (Figure 11.17).

Like the primary area, the secondary areas each contain a map of the body, with greater amounts of cortex devoted to the parts of the body that produce finer movements (Figure 11.18). The sequence of processing in the motor cortex is just the opposite of what we see in the sensory areas: Planning of movement begins in the association areas, and the primary motor cortex is the final cortical motor area. Along the way, a movement is modified by inputs from the somatosensory cortex, the posterior parietal cortex, the basal ganglia, and the cerebellum. As with many other functions, the prefrontal cortex plays an executive role, so it will receive our attention first. We will be covering several brain areas and their functions in the next few pages. It would be a good idea to review the summary in Table 11.2 before reading further, so that you will have an idea of where we are going.



Description

Figure 11.17 The Motor Areas of the Cortex and Cerebellum.
Connections between the primary motor cortex and the basal ganglia are not shown.



Description

Figure 11.18 The Primary Motor Area.
The homunculus shows the relative amount of cortex devoted to different parts of the body.

Source: Adapted from *The Cerebral Cortex of Man* by W. Penfield and T. Rasmussen, 1950, New York: Macmillan. © 1950 Gale, a part of Cengage Learning, Inc.

Table 11.2
TABLE 11.2 The Major Brain Areas of Movement and Their Functions.

STRUCTURE	FUNCTIONS
Prefrontal cortex	Selects the appropriate behavior and its target, using a combination of bodily and external information.
Premotor cortex	Combines information needed for movement programming, such as the target being reached for and its location, which arm to use, and the arm's location.
Supplementary motor area	Assembles sequences of movements, such as eating or playing the piano; coordinates movements between the two sides of the body (e.g., task sharing between the hands).
Primary motor cortex	Executes voluntary movements by organizing the activity of unspecialized cells; adds force and direction control.
Basal ganglia	Uses information from secondary areas and the somatosensory cortex to integrate and smooth movements; apparently involved in learning movement sequences.
Cerebellum	Maintains balance, refines movements, controls compensatory eye movements. Involved in learning motor skills.

The Prefrontal Cortex

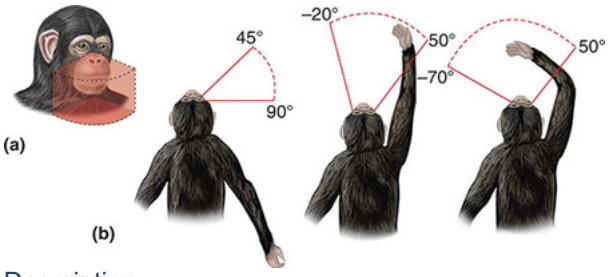
You already know two functions of the prefrontal cortex that suit it for its role in movement control: First, it plans actions with regard to their consequences; second, it receives information from the ventral visual stream about object identity, which is useful in identifying targets of motor activity. As an initial step in motor planning, the *prefrontal cortex* integrates sensory information about the world with information about the body (from the posterior parietal cortex); it then holds the information in memory while selecting the appropriate movement and its target (see Figure 11.17). Considering its activities, it really makes more sense to say that the role of the prefrontal cortex is not so much in planning movements as in planning *for* movements.

These functions are typically investigated in monkeys while they perform some variation of a *delayed match-to-sample task*. The monkey is presented with a visual stimulus; then, after a delay of a few seconds in which the stimulus is absent, the monkey is presented two or more stimuli and required to select the original stimulus (by reaching for it) to obtain a reward, such as a sip of juice. Some cells in the prefrontal cortex start firing when the first stimulus is presented and continue to fire throughout the delay, suggesting that they are "remembering" the stimulus. At response time, another group of prefrontal cells starts firing before activity starts in the premotor areas; this indicates that the prefrontal cortex selects the target of behavior and the appropriate motor responses (Goldman-Rakic, Bates, & Chafee, 1992; Hoshi, Shima, & Tanji, 2000; Rainer, Rao, & Miller, 1999).

? What is the relationship between the primary motor area and the association areas?

The Secondary Motor Areas

The **premotor cortex** begins programming a movement by combining information from the prefrontal cortex and the posterior parietal cortex (Kalaska & Rizzolatti, 2013). A good example comes from a study in which monkeys were cued to reach for one of two targets, A or B, in different locations and to use the left arm on some trials and the right arm on others. Some premotor neurons increased their firing rate only if target A was cued, and other neurons were selective for target B. Other cells fired selectively depending on which arm was to be used. Still other cells combined the information of the first two kinds of cells; they increased their firing only when a target was cued *and* a particular arm was to be used (Hoshi & Tanji, 2000). Two other cell types combine visual and somatosensory information to provide visual guidance of reaching and object manipulation. The first responds to visual stimuli on or near a specific part of the body, as in Figure 11.19a; another shifts the location of its visual receptive field to coincide with the location of the monkey's hand as it moves (Figure 11.19b; Graziano, Hu, & Gross, 1997; Graziano, Yap, & Gross, 1994).



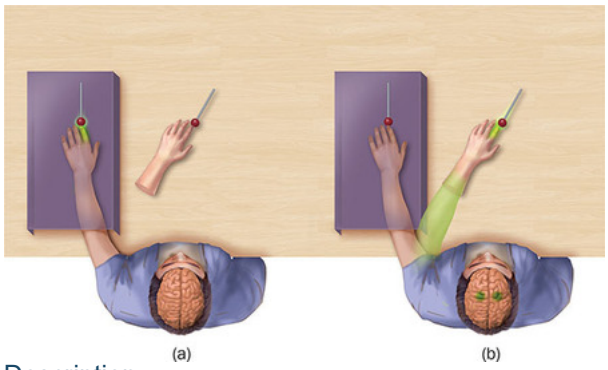
Description

Figure 11.19 Receptive Fields of Two Types of Premotor Neurons That Responded to Both Visual and Body Information.
(a) The receptive field of a cell that responded when a visual stimulus was in the area outlined near the face. (b) The visual field of the second type of neuron when the arm was out of sight. Middle and right, the visual field as the monkey's arm moved forward and across.

Source: Adapted from Figure 1 in "Coding of Visual Space by Premotor Neurons," by M. S. A. Graziano, G. S. Yap, and C. G. Gross, *Science, 266,* pp. 1054–1057. Copyright © 1979.

A fascinating demonstration of the role these specialized cells play occurs in a bizarre phenomenon known as the "rubber hand illusion." The individual sits at a table with the left hand hidden from view; the experimenter strokes the hidden left hand with a brush while simultaneously stroking a rubber hand, which is in full view (Figure 11.20). After a few seconds, the sensation seems to be coming from the rubber hand, which the subject identifies as "my hand." A study used fMRI to determine where the illusion occurs in the brain (Ehrsson, Spence, & Passingham, 2004). The posterior parietal cortex, which combines the visual and touch information, was active whether

the two hands were stroked in synchrony or in asynchrony. The premotor area, by contrast, became active only when the stroking was simultaneous, and only after the individual began to experience the illusion; moreover, the strength of activation was related to the intensity of the illusion reported by the subject.



Description

Figure 11.20 The Premotor Cortex and the Rubber Hand Illusion.
(a) The hidden left hand is stroked in synchrony with the fake hand, which is in full view. (b) After a few seconds, the individual feels that the sensation is coming from the rubber hand and reports a sense of ownership of the rubber hand (indicated by the light green outline). Apparently, the touch field and the visual field have become coordinated in the brain. fMRI recording shows that the premotor cortex is active during this illusion (indicated by the blue circles).

Source: From "Probing the Neural Basis of Body Ownership," by M. Botvinick, *Science, 305*, pp. 782–783, unnumbered figure on page 782. Illustration copyright © 2004 Taina Litwak. Used with permission.

Output from the prefrontal cortex flows to the **supplementary motor area**, which assembles sequences of movements, such as those involved in eating or in playing the piano. In monkeys trained to produce several different sets of movement sequences, different neurons increase their firing during a delay period depending on which sequence has been cued for performance (Shima & Tanji, 2000; Tanji & Shima, 1994). An important form of movement sequencing is the coordination of movements between the two sides of the body. For example, when a monkey's supplementary motor cortex is damaged in one hemisphere, its hands tend to duplicate each other's actions instead of sharing the task (C. Brinkman, 1984). Humans with similar damage also have trouble carrying out tasks that require alternation of movements between the two hands (Laplane, Talairach, Meininger, Bancaud, & Orgogozo, 1977). Coordinating the actions of the limbs is one of the biggest problems to be overcome on the way to developing mechanized prostheses, as A Further Look explains.

A Further Look:

Brain-Computer Interfaces

Source: Larry French/Getty Images Entertainment/Getty Images

Brain-controlled devices have been a science fiction trope for many years, such as the Russian thought-powered fighter jet in the 1977 book *Firefox* by Craig Thomas (and the 1982 Warner Brothers movie starring Clint Eastwood). So far, most of the success with brain-computer interfaces has been limited to movement of a single body part, such as using a robotic arm to take a drink of coffee or eat a bit of chocolate. Todd Kuiken at the Rehabilitation Institute of Chicago has developed a procedure called targeted reinnervation. The nerves that once served the muscles of the amputated limb are redirected to a “spare” muscle; the electrical signals generated when the individual activates this muscle are amplified and used to operate a motorized prosthesis. These devices, while much more advanced than the crude prosthetic limbs of a decade ago, are still in their infancy. They can restore motor function of a lost limb, but they lack both the sense of touch and the ability to regulate the amount of force used to pick up an object without damaging it. Kuiken and other research teams are now developing prosthetic hands with pressure sensors in the fingers that stimulate the reinnervated muscle groups and provide feedback that is perceived by the brain as touch sensations. An artificial leg developed by Hubert Egger at the University of Linz in Austria can provide amputees with the feeling of the texture of the ground the individual is standing on (R. Schwartz, 2015). More recently, the Department of Defense (DOD) awarded a $6 million grant to a Florida International University team led by Dr. Ranu Jung, which developed a prosthetic arm that taps into severed nerves (Baro, 2019). This procedure allows patients to experience touch and force experienced by the prosthetic fingertips, which means we’re inching closer to a full “bionic” replacement limb.

How about making these artificial limbs more realistic by using synthetic materials that act like natural tissues in the way they bend, flex, and change with increasing force? Hugh Herr, at the MIT Biomechatronics group, lost both legs from frostbite while mountain climbing. He is designing synthetic limb prosthetics with these more natural and flexible materials. The limbs use residual nerve signals to control the actions of the limbs, but the strength of those signals can modify the flexibility and force of the artificial limb (Humphries, 2015). More recently, Dario Farina and colleagues (2017) developed new prosthetic arms that are controlled by undamaged spinal motor neurons, allowing more signals to be received and permitting more extensive range of movements than traditional prosthetics permit. Volunteers in Farina’s study were able to open and close their hand, move their elbow joint, and move their wrist from side to side. More extensive clinical trials are the next step in developing these new prosthetics and making them available outside the research laboratory.

The Primary Motor Cortex

The **primary motor cortex** is responsible for the organization and execution of voluntary movements; its cells fire most during the movement instead of prior to it (G. E. Alexander & Crutcher, 1990; Riehle & Requin, 1989). Individual motor cortex cells are not reserved for a specific movement but contribute their function to a range of related behaviors; the primary motor cortex orchestrates the activity of these cells into a useful movement and contributes control of the movement's force and direction (Georgopoulos, Taira, & Lukashin, 1993; M. A. Maier, Bennett, Hepp-Reymond, & Lemon, 1993). This orchestration was particularly evident in a stimulation study by Graziano, Taylor, and Moore (2002). Instead of using the usual brief pulses of electricity, which produce only muscle twitches, they increased the duration to a half-second and saw complex, coordinated responses in the monkeys, such as grasping, moving the hand to the mouth, and opening the mouth. The primary motor cortex can put these complex movement sequences together with the aid of input from the secondary motor areas, the somatosensory cortex, and the posterior parietal area (see Figure 11.17; Kalaska & Rizzolatti, 2013). Presumably, information from the somatosensory and posterior parietal areas provides feedback needed for refining movements on the fly.

The Basal Ganglia and Cerebellum

The basal ganglia and cerebellum produce no motor acts themselves. Rather, they modulate the activity of cortical and brain stem motor systems; in that role, they are necessary for posture and smooth movement (Wolpert, Pearson, & Ghez, 2013). The **basal ganglia**—the caudate nucleus, putamen, globus pallidus, and the substantia nigra—use information from the primary and secondary motor areas and the somatosensory cortex to integrate and smooth movements. The basal ganglia send output directly to the primary motor cortex and supplementary motor area and to the premotor cortex via the thalamus. As you can see in Figure 11.21, these structures border the thalamus; they apparently smooth movements through both facilitating and inhibitory outputs to the thalamus (Wichmann & DeLong, 2013). The basal ganglia also are especially active during complex sequences of movements (Boecker et al., 1998). It appears that they are involved in learning movement sequences so that the movements can be performed as a unit (Graybiel, 1998). In fact, one of the symptoms of Parkinson's disease, which is caused by degeneration in the basal ganglia, is impaired learning, whether motor behavior is involved or not (Knowlton, Mangels, & Squire, 1996). Malfunction in the basal ganglia results in postural abnormalities and involuntary movements in Parkinson's disease and Huntington's disease, which can be treated using deep brain stimulation (see Wichmann & DeLong, 2016).

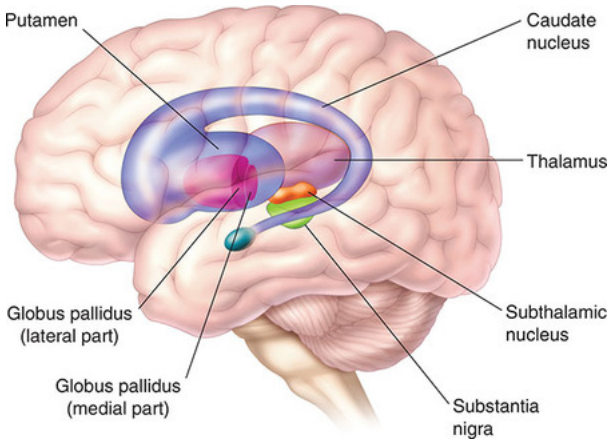


Figure 11.21 The Basal Ganglia.
The basal ganglia include the caudate nucleus, putamen, and globus pallidus.

What do the basal ganglia and cerebellum add?

When the *cerebellum* receives information from the motor cortex about an intended movement, it determines the order of muscular contractions and their precise timing. It also uses information from the vestibular system to maintain posture and balance, refine movements, and control eye movements that compensate for head movements (Lisberger & Thach, 2013). Once an intended movement has been modified, the cerebellum sends the information back to the primary motor cortex. We can see the contribution of the cerebellum in the deficits that occur when it is damaged. For example, we begin to shape our hand for grasping while the arm is moving toward the target, but a person with cerebellar damage reaches, pauses, and then shapes the hand. A normal individual touches the nose in what appears to be a single, smooth movement; cerebellar damage results in exaggerated, wavering corrections. The effects of cerebellar damage on coordination and accuracy in limb movements is like the effect of alcohol; the drunk driver who is pulled over by the police has trouble walking a straight line, standing on one foot with the eyes closed, or touching the nose with the tip of the finger. People with damage to the cerebellum are often mistakenly believed to be drunk.

The cerebellum lives up to the meaning of its name, “little brain,” by applying its expertise to a variety of tasks. It is necessary for learning motor skills (D. A. McCormick & Thompson, 1984), but it also participates in nonmotor learning (Canavan, Sprengelmeyer, Diener, & Hömberg, 1994) and in making time and speed judgments about auditory and visual stimuli (Keele & Ivry, 1990). Also, patients with cerebellar damage have difficulty shifting visual attention to another location in space (whether this involves eye movements or not), taking 0.8 to 1.2 seconds, compared with 0.1 second for normal individuals (Townsend et al., 1999). We should think of the cerebellum in terms of its general functions, rather than strictly as a motor organ.

Disorders of Movement

You might think that anything as complex as the movement system would be subject to malfunction; if so, you would be correct. Predictably, movement disorders are devastating to their victims. We will consider as representatives of these diseases Parkinson’s disease, Huntington’s disease, myasthenia gravis, and multiple sclerosis.

Parkinson’s Disease

As we mentioned at the beginning of this chapter, **Parkinson’s disease** is characterized by motor tremors, rigidity, loss of balance and coordination, and difficulty in moving, especially in initiating movements (Olanow & Tatton, 1999; Youdim & Riederer, 1997). Parkinson’s affects about 0.3% of the population in industrialized countries and 1% of people over the age of 60 years (Nussbaum & Ellis, 2003). The symptoms are caused by deterioration of the **substantia nigra**, whose neurons send dopamine-releasing axons to the **striatum**, which is composed of the basal ganglia’s caudate nucleus and putamen and the nucleus accumbens. In something less than 10% of cases, the disease is **familial**, meaning that it occurs more frequently among relatives of a person with the disease than it does in the population (Greenamyre & Hastings, 2004). If a member of a twin pair is diagnosed with Parkinson’s disease before the age of 51, the chance of an identical twin also having Parkinson’s is six times greater than it is for a fraternal twin (Tanner et al., 1999). The same study found no evidence of a genetic influence in individuals whose symptoms developed later in life; we will look at possible non-genetic causes shortly. Geneticists have located 28 chromosomal regions that are most likely related to Parkinson’s disease, and 6 of those regions contain genes whose mutations are known to cause the disease on their own (reviewed in Klein & Westenberger, 2012). These six play many roles in cellular functioning and protein synthesis, and at least two are associated with the presence of **Lewy bodies**, abnormal clumps of protein that form within neurons (Figure 11.22). Lewy bodies are often found in Parkinson’s patients as well as in patients with two forms of dementia, Alzheimer’s disease and dementia with Lewy bodies (Glasson et al., 2000; Spillantini et al., 1997). Lewy bodies probably contribute to the cognitive deficits and depression that often accompany Parkinson’s disease; they may represent the brain’s attempt to remove

proteins that have been damaged by toxins. The patient's complement of genes helps determine age of onset, rate of progression, and whether cognitive loss will be a part of the disease progression. Actor Robin Williams and television personality Casey Kasem had been diagnosed with Parkinson's disease, and each showed signs of the disorder dementia with Lewy bodies prior to their deaths (McKeith, 2015; Savica, 2014).

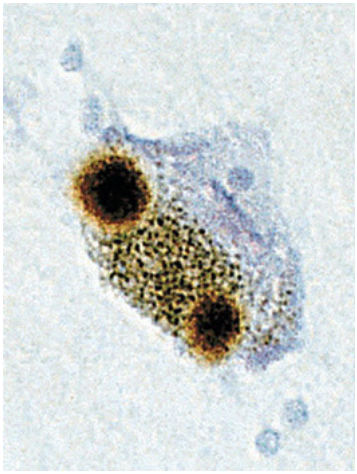


Figure 11.22 Lewy Bodies in a Brain With Parkinson's Disease.
A neuron containing two stained Lewy bodies, abnormal clumps of protein.

Source: α-Synuclein in Lewy Bodies," by M. G. Spillantini et al., 1997, Nature 388, 839–840. Copyright © 1997. Used with permission.

? What are the causes and effects of the movement disorders?

Several environmental influences have been implicated in Parkinson's disease. One cause is subtle brain injury; being knocked unconscious once increases the risk by 32%, and the risk rises by 174% for those knocked out several times. Other research points to a variety of toxins, including industrial chemicals, carbon monoxide, herbicides, and pesticides (Olanow & Tatton, 1999). Numerous studies show an association between pesticide use and Parkinson's, but the human studies are correlational, and establishing a causal relationship has been difficult (reviewed in Moretto & Colosio, 2013). Pesticide exposure produces some of the symptoms of Parkinson's in animals, though with very high dosages. These studies also suggest that specific genes increase sensitivity to the toxic effects, providing another example of the interaction between hereditary and environmental effects. While firm conclusions have eluded us, a study in California's highly agricultural Central Valley that found a tripling of risk with occupational exposure to the pesticides ziram, maneb, and paraquat (A. Wang et al., 2011) suggests extreme caution while we try to sort things out.

Interestingly, the risk of Parkinson's disease is reduced as much as 80% in coffee drinkers (G. W. Ross et al., 2000). The risk also drops by 50% in smokers (Fratiglioni & Wang, 2000), but, of course, no benefit of smoking outweighs its dangers. Rat studies indicate that cigarette smoke may prevent the accumulation of neurotoxins (Soto-Otero, Méndez-Álvarez, Sánchez-Sellero, Cruz-Landeira, & López-Rivadulla, 2001) and that caffeine reduces the effect of neurotoxins by blocking adenosine receptors, which, as we saw in Chapter 5, results in increased dopamine and acetylcholine release (J.-F. Chen et al., 2001). In heavy coffee drinkers, a variant of the glutamate receptor gene *GRIN2A* reduces Parkinson's risk by 59% (Hamza et al., 2011). There has been some clinical success in treating Parkinson's with adenosine and glutamate receptor antagonists (Gasparini, Di Paolo, & Gomez-Mancilla, 2013; Hickey & Stacy, 2012), and one drug (istradefylline) has been approved by the FDA for use in combination with traditional dopamine treatments discussed below (U.S. Food and Drug Administration, 2019).

?

How can we treat symptoms of Parkinson's disease?

Parkinson's disease is typically treated by administering **levodopa (L-dopa)**, which is the precursor for dopamine. Parkinson's tends to be more severe in men than in women, presumably because estrogen indirectly raises dopamine levels (Haaxma et al., 2007). Dopamine will not cross the blood-brain barrier, but L-dopa will, and the brain converts it to dopamine. Dopamine agonists can also be helpful, and even placebos increase dopamine release (de la Fuente-Fernández et al., 2001). But these treatments increase dopamine throughout the brain, which causes side effects ranging from restlessness and involuntary movements to hallucinations. Also, as more neurons die, more of the drug is required, which increases the side effects. While L-dopa remains the standard, its side effects mean that some patients are forced to use other drugs. Unfortunately, these drugs also treat only some of the symptoms and with limited benefit.

Early attempts showed that implanted embryonic neural cells could survive in the striatum and produce dopamine (Figure 11.23; C. R. Freed et al., 2001; Greene & Fahn, 2002). However, behavioral improvement was not clinically significant, and some of the patients developed involuntary movements, apparently due to excess dopamine. More recent work using adult neural stem cells resulted in more than 80% improvement in motor behavior ratings; the improvement held up for 3 years but had disappeared at the end of 5 years (Lévesque, Neuman, & Rezak, 2009). Clinical application is hampered by immune reactions to stem cells and by the development of tumors at the implant site. More recent work indicates that immune response is minimal with stem cells taken from the individual (Morizane et al., 2013), and tumor development can be avoided by allowing the stem cells to mature into an early form of neural cell before implanting (Doi et al., 2012). Gene therapy has also been tried experimentally, with the intent of increasing dopamine levels or reducing excess activity in affected brain areas. Results have been mixed in the handful of clinical trials conducted at the Phase 1 and Phase 2 levels; so far, no procedure has reached the critical Phase 3 level that could establish its effectiveness sufficiently for approval by the FDA (Denyer & Douglas, 2012). To avoid previous disappointments, the British company Oxford Biomedica has used a procedure called ProSavin to deliver a combination of three genes into the striatum to increase dopamine production there; all 15 drug-resistant patients improved in motor capability and continued improving for 5 years after a Phase 1/Phase 2 safety and dosage trial (Palfi et al., 2018). These procedures are still in their infancy; we need to remember that the first several heart transplant operations failed, but they are almost routine today.

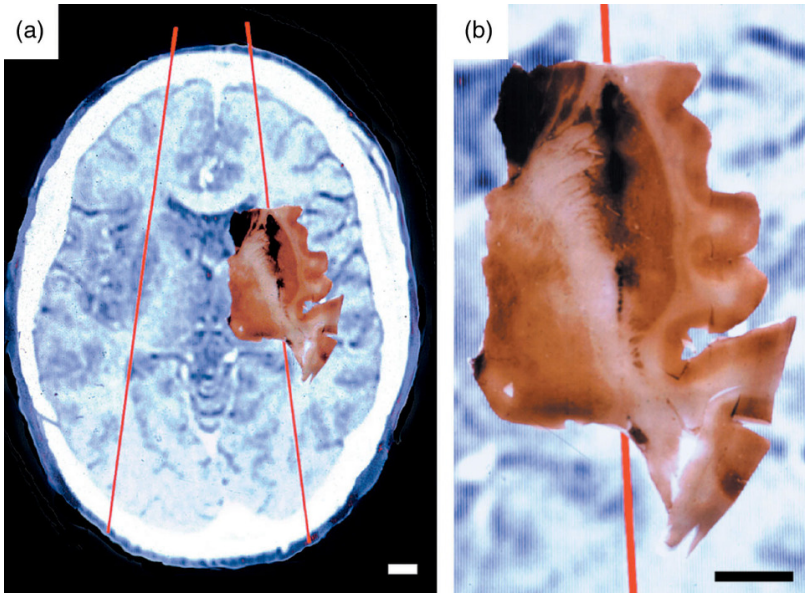


Figure 11.23 Transplanted Embryonic Cells in the Brain of a Parkinson's Patient. The patient died in a car accident 7 months after her surgery. (a) Her right putamen

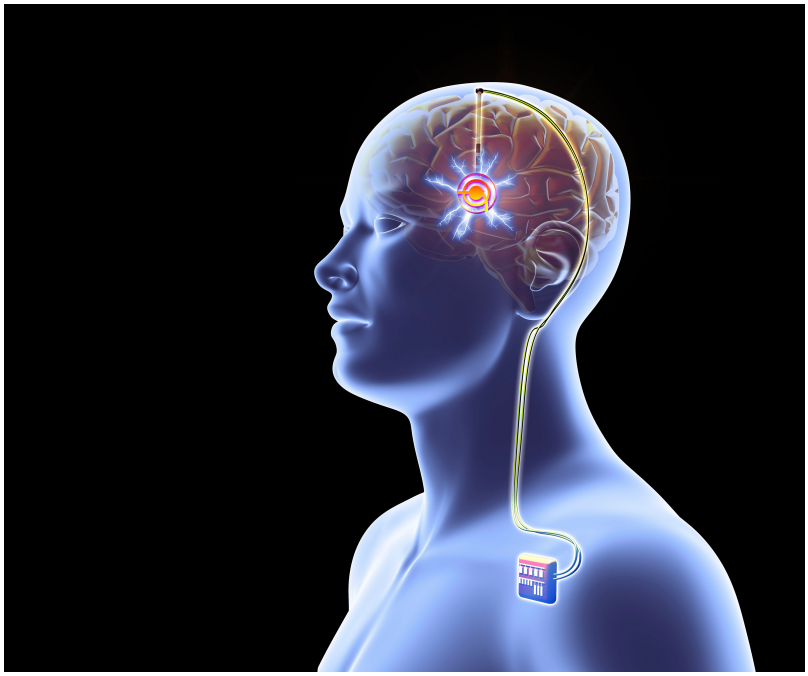
(part of the striatum) was removed and placed on a photograph of the magnetic resonance image of her brain made at the time of surgery. The red lines indicate the angle at which the needles were inserted into the brain to inject the fetal cells (right side of the brain) and as a control procedure (left side). The dark area on the putamen along the needle track is due to the staining of new dopamine cells and shows that the axons had grown 2 to 3 millimeters from the cell bodies. The image in (b) is an enlargement of the putamen.

Source: "Transplantation of Embryonic Dopamine Neurons for Severe Parkinson's Disease," by C. R. Freed et al., 2001, New England Journal of Medicine, 344, 710–719, fig. 3 a and b, p. 717. Reprinted with permission.

Frustration with therapeutic alternatives is creating something of a revival in surgical treatments, which were largely abandoned when drugs for Parkinson's disease became available (Cosgrove & Eskandar, 1998). Strategically placed lesions in the subthalamic nucleus and the globus pallidus, both in the basal ganglia (see Figure 11.21), have provided some improvement for patients who have difficulty using dopaminergic drugs (Cosgrove & Eskandar, 1998). Michael J. Fox had such lesions, and they vastly improved his ability to control his movement (M. J. Fox, 2002). These two structures produce a rhythmic bursting activity like the rhythmic activity in parkinsonian tremors, which apparently explains why destroying them reduces this symptom (Perkel & Farries, 2000). But the surgery can damage adjacent structures, resulting in other deficits, such as weakness in a part of the body. More recently, physicians are turning to a less drastic procedure known as **deep brain stimulation (DBS)**, in which electrical stimulation through implanted electrodes is used to trigger dopamine release in areas deprived of that neurotransmitter. While effective, there is a risk of weight gain due to an increased sensitivity to the pleasurable aspects of food, similar to the weight gain seen with dopamine-increasing drugs. A Further Look describes how DBS works, along with additional risks.

A Further Look:

Deep Brain Stimulation and Parkinson's Disease



Source: Pasieka / Science Source

Although almost 30 years old, an effective treatment for the motor tremors and repetitive movements seen in Parkinson's disease patients continues to be a procedure called deep brain stimulation (DBS). The mechanism by which DBS works is to block electrical signals that are responsible for the tremors associated with Parkinson's. In this technique, neurosurgeons implant electrodes into the brain and run insulated wires under the skin down the neck into the upper chest area. There, the wires are attached to a pacemaker-like device that is also implanted into the patient's chest. In this way, a precise set of electrical pulses can be sent to the target area (usually the basal ganglia) to "reset" activity in the brain area(s) and restore normal function. After a set of stimulations, tremor usually dissipates within seconds (Blahak et al., 2009), whereas effective treatment for dystonia (uncontrollable repetitive muscle contractions) may take additional months of treatment.

So what does DBS do in the brain? There's a lot of debate as to what exactly the stimulation does to improve motor function. Early research concluded the stimulation temporarily knocked out neurons in the stimulation site (like a reversible lesion; Wichmann, Bergman, & DeLong, 1994), but later teams suggested the added electrical charges made dendritic inputs stronger (McIntyre, Grill, Sherman, & Thakor, 2004). Other findings suggest an increase in chemical neurotransmitters such as adenosine (Bekar et al., 2008) and dopamine (Gale et al., 2013). Improved motor functioning, allowing L-dopa reduction, has been reported for as long as 10 years (reviewed in Fasano, Daniele, & Albanese, 2012). Results are mixed regarding reducing cognitive deficits, which often are more disabling and resistant to treatment than the motor symptoms. DBS usually improves or eliminates impulse control problems in the 13% to 16% of patients affected, possibly due to L-dopa reduction.

This improvement does carry some risk: Some studies have reported the onset of pathological gambling, hypersexuality, and compulsive eating. Recent work has suggested that side effects of DBS of the subthalamic nucleus include increased impulsivity and sensitivity to food rewards, resulting in undesired weight gain, which indicates that the neurons and circuits play a role in multiple behaviors. In addition, there is some loss of verbal fluency after DBS, and apathy increases in some patients.

Huntington's Disease

Like Parkinson's disease, **Huntington's disease** is a degenerative disorder of the motor system involving cell loss in the striatum and cortex. Years before a diagnosis, Huntington's disease begins with mild, infrequent jerky movements that result from impaired error correction (M. A. Smith, Brandt, & Shadmehr, 2000). Later, involuntary movements appear, first as fidgeting and then as movements of the limbs and, finally, writhing of the body and facial grimacing. Because these movements sometimes resemble a dance, Huntington's disease is also called Huntington's chorea, from the Greek word *choreia*, which means "dance." The patient loses the ability to carry out daily activities. Death usually follows within 15 to 30 years after the onset of the disease.

Unlike Parkinson's disease, cognitive and emotional deficits are a universal characteristic of Huntington's disease. These deficits include impaired judgment, difficulty with a variety of cognitive tasks, depression, and personality changes. The motor symptoms are due to the degeneration of inhibitory GABA-releasing neurons in the striatum, whereas defective or degenerated neurons in the cortex probably account for the psychological symptoms (Figure 11.24; J. B. Martin, 1987; Tabrizi et al., 1999).

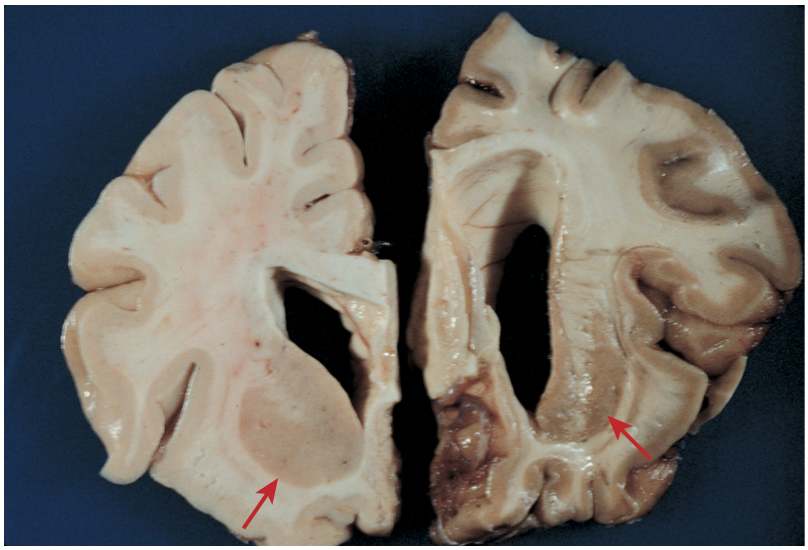


Figure 11.24 Loss of Brain Tissue in Huntington's Disease.
Left, a section from a normal brain; right, a section from a person with Huntington's disease. The enlarged lateral ventricle in the diseased brain is due to loss of neurons in the caudate nuclei (arrows).

Source: Courtesy of Robert E. Schmidt, Washington University.

Huntington's disease results from a mutated form of the *huntingtin* gene (Huntington's Disease Collaborative Research Group, 1993). The loss of neurons is probably due to the accumulation of the gene's protein, also known as huntingtin, whose function is unknown (DiFiglia et al., 1997). In normal individuals, the gene has less than 26 repetitions of the bases cytosine, adenine, and guanine (CAG repeats; see Chapter 1). The more repeats the person has beyond 26, the earlier in life the person will succumb to the disease (F. O. Walker, 2007). Because the gene is dominant, a person who has a parent with Huntington's has a 50% chance of developing the disease. This is an unusual example of a human disorder resulting from a single gene.

Numerous drugs are used to treat the various symptoms, including antidepressants and antipsychotics, but only one (Tetrabenazine) has been approved specifically for Huntington's disease by the FDA. It reduces the excess dopamine that causes the abnormal movements. Drugs that silence the *huntingtin* gene are showing promise in animals; a single injection of one of these drugs normalized movement in mice for the 9-month duration of the study and significantly reduced *huntingtin* protein levels for 8 weeks in monkeys (Kordasiewicz et al., 2012). Grafting of fetal striatal cells has so far produced only modest and temporary improvement (Cicchetti et al., 2009), but a recent method that converts astrocytes (a type of glial cell) into neurons improved function and extended life in a mouse model (Bryson, 2020).

Autoimmune Diseases

Myasthenia gravis (MG) is a disorder of muscular weakness caused by reduced numbers or sensitivity of acetylcholine receptors. The muscle weakness can be so extreme that the patient has to be maintained on a respirator. In fact, 25 years ago, the mortality rate from MG was about 33%; now few patients die from the disease, thanks to improved treatment (R. H. Brown, Cannon, & Rowland, 2013).

The loss of receptors was demonstrated in an interesting way. The venom of the many-banded Formosan krait, a very poisonous snake from Taiwan, paralyzes prey by binding to the acetylcholine receptor. When the venom's toxin is labeled with radioactive iodine and applied to a sample of muscle tissue, it allows researchers to

identify and count the acetylcholine receptors. The MG patients turned out to have 70% to 90% fewer receptors than normal individuals (Fambrough, Drachman, & Satyamurti, 1973). Drugs that inhibit the action of acetylcholinesterase give temporary relief from the symptoms of MG (Figure 11.25; Rowland, Hoefer, & Aranow, 1960). Remember from Chapter 2 that acetylcholinesterase breaks down acetylcholine at the synapse; these inhibitors increase the amount of available neurotransmitter at the neuron-muscle junction.

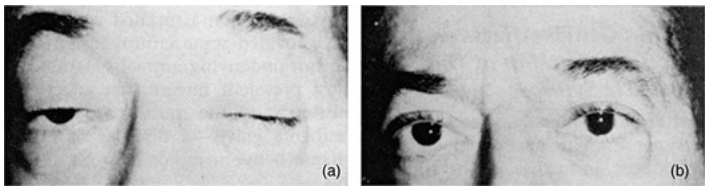


Figure 11.25 Effect of an Acetylcholinesterase Inhibitor on Myasthenia Gravis. (a) Patients often have drooping eyelids, as shown here. This patient also could not move his eyes to look to the side. (b) The same patient one minute after injection of an acetylcholinesterase inhibitor. The eyes are open and able to move freely.

Source: "Mysathenic Syndromes," by L. P. Rowland, P. F. A. Hoefer, and H. Aranow, Jr., 1960, Research Publications-Association for Research in Nervous and Mental Disease, 38, 547–560. Reprinted with permission of Wolters Kluwer.

Although immune system therapy has sometimes been used (Shah & Lisak, 1993), removal of the thymus (thymectomy) has now become a standard treatment for MG (R. H. Brown et al., 2013). The thymus is the major source of lymphocytes that produce antibodies. Improvement can take years, but thymectomy eliminates symptoms completely in almost 80% of patients and reduces them in another 13% to 17% (Ashour et al., 1995; Jaretzki et al., 1988).

Multiple sclerosis (MS) is a motor disorder with many varied symptoms, caused by deterioration of myelin (demyelination) and neuron loss in the central nervous system. In Chapter 2, you saw that demyelination causes slowing or elimination of neural impulses. Demyelination thus reduces the speed and strength of movements. Even before that happens, impulses traveling in adjacent neurons, which should arrive simultaneously, become desynchronized because of differential loss of myelin. An early sign of the disorder is impairment of functions that require synchronous bursts of neural activity, such as tendon reflexes and vibratory sensation (R. H. Brown et al., 2013). As the disease progresses, unmyelinated neurons die, leaving areas of *sclerosis*, or hardened scar tissue (Figure 11.26). As a result, the person experiences muscular weakness, tremor, pain, impaired coordination, urinary incontinence, and visual problems. Studies indicate that neuron loss is more important than previously thought and suggest that the loss results from a degenerative process in addition to the demyelination (G. C. DeLuca, Ebers, & Esiri, 2004; De Stefano et al., 2003).

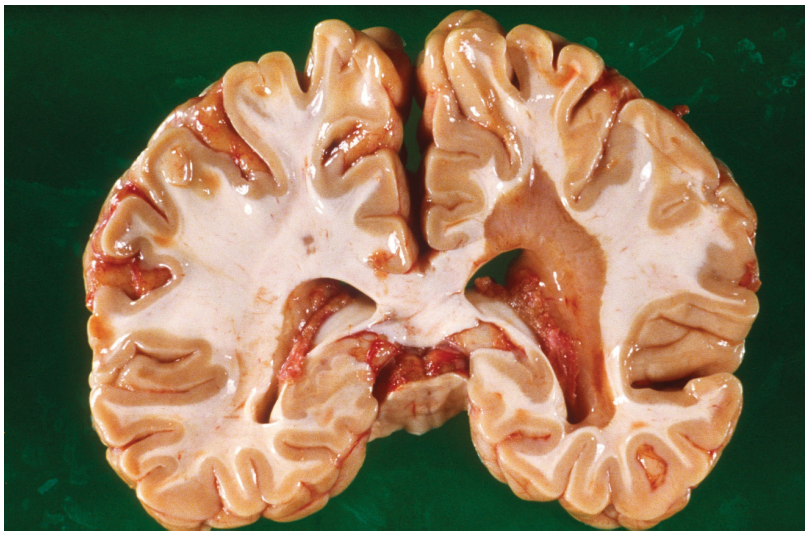


Figure 11.26 The Brain of a Deceased Multiple Sclerosis Patient.
Area adjacent to the ventricle is demyelinated neurons and scar tissue.

Biophoto Associates / Science Source

Like MG, MS is an autoimmune disease. Injecting foreign myelin protein into the brains of animals produces symptoms like those of MS (Wekerle, 1993), and T cells that are reactive to myelin proteins (see Chapter 8) have been found in the blood of MS patients (Allegretta, Nicklas, Sriram, & Albertini, 1990). A genome-wide study has implicated various immune system genes in MS (International Multiple Sclerosis Genetics Consortium, 2007), but some environmental conditions may be needed to trigger the immune attack on myelin. One possibility is that the immune system has been sensitized by an earlier viral infection; for example, studies have found antibodies for Epstein-Barr virus in MS patients (H. J. Wagner et al., 2000), and patients more often had mumps or measles during adolescence (Hernán, Zhang, Lipworth, Olek, & Ascherio, 2001).

Although many drugs are available to treat the various symptoms of the disease, only a few drugs modify the problematic immune activity in MS patients; these immune-suppressing drugs slow the progression but do not repair the harm already done. A drug that blocks voltage-gated potassium channels, dalfampridine, helps demyelinated axons transmit signals by increasing the strength of action potentials; it improves motor performance, particularly walking (Jeffrey, 2010), but it can increase the risk of seizures (U.S. Food and Drug Administration, 2012). In a multicenter stem cell study, 281 patients with progressive MS were treated by harvesting stem cells from their bone marrow, wiping out their immune systems using chemotherapy, and then injecting the stem cells back; 46% of the patients had no additional symptoms 5 years afterward (Muraro et al., 2017).

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- Explain how antagonistic muscles and spinal reflexes maintain posture.
- What contribution does each of the cortical motor areas make to movement?
- Make a diagram showing how you think the neurons would be interconnected to carry out the target and arm selection task described in the Hoshi and Tanji study on page 373.

- What are the genetic and environmental causes of the movement disorders described in this chapter?

IN PERSPECTIVE

Unless we have a disorder like Michael J. Fox does (described in the chapter introduction), we usually take our body senses and our capability for movement for granted. And yet just standing upright is a remarkable feat. Granted, a mechanical robot could do it easily, but only if it had a rigid body like C-3PO from *Star Wars*. If the robot had our flexibility of movement and posture, it would have to devote a fair amount of its computer brain to making split-millisecond adjustments to avoid toppling over from a strong wind. Then another chunk of its computer would be required just to locate a visual object in space, to reach out smoothly and quickly for the object, and to shape its hand for grasping, deciding whether to use the whole hand or the finger and thumb, how much pressure to apply, and so on. You get the idea. Better to let a human do it, because all that fancy equipment comes standard on the basic model—which is why C-3PO was not a real droid but actor Anthony Daniels in a suit.

Now you see why so much of the brain is concerned with the sensory and motor components of movement. And when the system becomes damaged, even the easiest behaviors become quite difficult. It is a wonder that we have enough left over for the demands of learning, intelligence, and consciousness, but as you will see in the remaining chapters, we do.

Chapter Summary

The Body Senses

- The body senses include proprioception, which tells us about the position and movement of our limbs and body; the skin senses, which inform us about the conditions in the periphery of our body; and the vestibular sense, which contributes information about head position and movement and helps us maintain balance.
- The skin senses—touch, warmth, cold, and pain—tell us about conditions at the body surface and about objects in contact with our body.
- The body senses are processed in a series of structures in the primary and secondary somatosensory cortex and in the posterior parietal cortex, with several similarities to visual processing. Pain processing also extends into additional areas.
- In their quest to find better ways of relieving pain, researchers have learned how the nervous system detects painful stimulation and found that the body has its own ways of relieving pain. Chronic pain presents particularly difficult challenges.

Movement

- There are three types of muscles: cardiac (heart), smooth (internal organs and blood vessels), and skeletal (striated) muscles.
- Spinal reflexes produce quick responses and provide postural adjustments. Central pattern generators provide routines, such as rhythmic walking movements.
- Cortical motor areas assess spatial and body information and construct movements by passing information through a succession of brain areas.
- The basal ganglia and cerebellum refine movements produced by the motor cortex.
- Several diseases attack the motor system at various points of vulnerability. Major causes that have been implicated are heredity, toxins, and autoimmune disorders.

Study Resources

For Further Thought

- Of proprioception, the vestibular sense, pain, and the other skin senses, which do you think you could most afford to give up? Why?
- If pain is beneficial, why does the body have pain relief mechanisms?
- Imagine a robot with a humanlike body. It is programmed to walk, reach, grasp, and so on. It has visual and auditory capabilities but no body senses. What would its movement be like?

- Judging by the examples given of movement disorders, what are the points of vulnerability in the motor system?

Test Your Understanding

1. Explain how endorphins relieve pain, describing the receptors and the pathway from the periaqueductal gray; include how we determine whether pain relief is endorphin based.
2. Walking barefoot, you step on a sharp rock. You reflexively withdraw your foot, plant it firmly on the ground again, and regain your posture. Describe these behaviors in terms of the sensory/pain mechanisms and reflexes involved.
3. Trace the progress of a movement through the parietal and frontal lobes, giving the names of the structures and a general idea of the processing occurring in each.
4. Compare the symptoms, causes, and treatment options for Parkinson's and Huntington's diseases.

Select the best answer:

1. Proprioception gives us information about
    1. conditions at the surface of our skin.
    2. conditions in the internal organs.
    3. the position and movement of our limbs and body.
    4. balance and the head's position and movement.
2. The skin senses include
    1. touch, warmth, and cold.
    2. touch, temperature, and pain.
    3. touch, temperature, movement, and pain.
    4. touch, warmth, cold, and pain.
3. Sharp pain and dull pain are due primarily to
    1. different kinds of injury.
    2. pain neurons with different characteristics.
    3. the passage of time.
    4. the person's attention to the pain.
4. According to Melzack and Wall, pressing the skin near a wound reduces pain by
    1. triggering inhibition in the pain pathway.
    2. triggering pain messages from nearby areas.
    3. releasing endorphins into the brain.
    4. releasing histamine into the wound area.
5. Endorphins
    1. activate the same receptors as opiate drugs.
    2. occupy receptors for pain neurotransmitters.
    3. block reuptake of pain neurotransmitters.
    4. inhibit brain centers that process pain emotion.
6. Both congenital pain insensitivity and chronic pain involve
    1. developmental alterations of brain areas responsible for the emotion of pain.
    2. alterations in the myelination of pain fibers.
    3. gene-mediated alterations of pain sensitivity.
    4. variations in the amount of substance P available.
7. Research suggests phantom pain is due to
    1. the patient's anxiety over the limb loss.
    2. memory of the pain of injury or disease that prompted the amputation.
    3. activity in severed nerve endings in the stump.
    4. neural reorganization in the somatosensory area.
8. Without a posterior parietal cortex, we would be most impaired in
    1. moving.
    2. making smooth movements.
    3. orienting movements to objects in space.
    4. awareness of spontaneously occurring movements.
9. If the nerves providing sensory feedback from the legs were cut, we would
    1. be able to walk but not run.
    2. have trouble standing upright.

3. lose strength in our legs.
4. quickly lose muscle mass in our legs.
5. not be able to move our legs.

10. A monkey is presented a stimulus and then must wait a few seconds before it can reach to the correct stimulus. Activity in the secondary motor area during the delay suggests that this area
    1. prepares for the movement.
    2. initiates the movement.
    3. executes the movement.
    4. All of these
11. Cells in the premotor cortex would be particularly involved when you
    1. remember a visual stimulus during a delay period.
    2. catch a fly ball.
    3. start to play a series of notes on the piano.
    4. execute a movement.
12. The primary motor cortex is most involved in
    1. combining sensory inputs.
    2. planning movements.
    3. preparing movements.
    4. executing movements.
13. The basal ganglia and the cerebellum produce
    1. no movements.
    2. movements requiring extra force.
    3. reflexive movements.
    4. sequences of movements.
14. Parkinson's disease is characterized most by
    1. deterioration of the myelin sheath.
    2. dancelike involuntary movements.
    3. deterioration of dopamine-releasing neurons.
    4. immune system attack on acetylcholine receptors.
15. Results of removing the thymus gland suggest that myasthenia gravis is a(n) _____ disease.
    1. genetic
    2. autoimmune
    3. virus-caused
    4. degenerative

Answers:

1. c, 2. d, 3. b, 4. a, 5. a, 6. c, 7. d, 8. c, 9. b, 10. a, 11. b, 12. d, 13. a, 14. c, 15. b.

For Further Reading

1. *Lucky Man*, by Michael J. Fox (Hyperion, 2002), details the actor's initial diagnosis, his struggle to balance life and work, and how he decided that helping others was more important than helping himself. For Fox's more up-to-date view on aging, mortality, and the stresses of living with Parkinson's disease, consider *No Time Like the Future: An Optimist Considers Mortality* (Flatiron, 2020).
2. *Awakenings*, by Oliver Sacks (Vintage Books, 1999), describes Dr. Sacks's early experiments in using L-dopa to treat the symptom of parkinsonism in patients with sleeping sickness. The movie of the same name, with Robin Williams, was based on this book.
3. *Phantoms in the Brain*, by V. S. Ramachandran and Sandra Blakeslee (HarperPerennial, 1999), called "enthralling" by the *New York Times* and "splendid" by Francis Crick, uses numerous (often strange) cases to explain people's perception of their bodies.
4. *Wall and Melzack's Textbook of Pain*, edited by Stephen McMahon, Martin Koltzenburg, Irene Tracey, and Dennis Turk (6th ed., Saunders, 2013), and *The Massachusetts General Hospital Handbook of Pain Management*, edited by Jane Ballantyne and in current use at the hospital (3rd ed., Lippincott Williams and Wilkins, 2005), are technical references on pain and pain management.
5. *Teaching Motor Skills to Children With Cerebral Palsy and Similar Movement Disorders: A Guide for Parents and Professionals*, by Sieglinde Martin

(Woodbine House, 2016), covers the treatment of movement disorders in an easy-to-understand format. If you find yourself working with children with movement disorders, this may be an inexpensive but very useful guide to working with children, planning evaluations, and understanding how therapy works.

Key Terms

antagonistic muscles 369

apotemnophilia 361

basal ganglia 376

body integrity identity disorder 361

cardiac muscles 369

central pattern generator (CPG) 371

chronic pain 365

deep brain stimulation (DBS) 379

dermatome 358

familial 377

gate control theory 364

Golgi tendon organs 371

Huntington's disease 380

inflammatory soup 361

levodopa (L-dopa) 378

Lewy bodies 377

multiple sclerosis (MS) 382

muscle spindles 370

myasthenia gravis (MG) 381

out-of-body experience 361

Parkinson's disease 377

periaqueductal gray (PAG) 364

phantom pain 367

posterior parietal cortex 360

premotor cortex 373

primary motor cortex 376

proprioception 354

secondary somatosensory cortex 360

skeletal muscles 369

skin senses 354

smooth muscles 369

somatosensory cortex 358

somatotopic map 358

striatum 377

substance P 362

substantia nigra 377

supplementary motor area 374

vestibular sense 356

Descriptions of Images and Figures

Back to Figure

1. The vestibular nerve is attached to utricle, saccule, and semicircular canals, the cochlea is wound around the cochlear nerve, and the facial nerve is between the vestibular nerve and the cochlear nerve.
2. Cross section of the semicircular canal shows that the cupula inside it is displaced in the direction of endolymph flow. The direction of acceleration is in opposite direction.
3. The layers of the inner surface of saccule, from the outermost to innermost, are otoliths, gelatinous material, hair cells, and neurons.

Back to Figure

The location of the dermatomes are as follows.

- 1, 2, and 3: On face from top to bottom
- C 2: Jaw
- C 3: Throat
- C 4: Neck
- C 5: Upper chest, lateral side of upper arm, and middle of forearm
- C 6: Medial side of forearm
- C 7: Dorsal surface of hand and middle of inner palm
- C 8: Lateral side of forearm
- T 1: Upper chest and medial side of the arms
- T 2: Upper chest and medial side of the upper arm
- T 3 through T 12: Trunk
- L 1: Hips

- L 2: Waist and inner thighs
- L 3: Thighs and knees
- L 4: Medial side of the lower leg
- L 5: Front of the lower leg
- S 1: Lateral side of the lower leg
- S 2: Back of the leg and testicles
- S 3: Genitals

Sensory neurons from the skin pass through the spinal cord, medulla, and thalamus, and reach the somatosensory cortex.
Back to Figure

1. The lateral fissure divides the frontal lobe and the temporal lobe. The primary motor cortex is on the superior side of the frontal lobe. The primary somatosensory cortex is on the anterior side of the parietal lobe. The cortices are separated by the central sulcus. The secondary somatosensory cortex is on the posteroinferior side of the primary somatosensory cortex. The posterior parietal cortex is on the posterior side of the parietal lobe.
2. A slice from the somatosensory cortex is labeled with body parts and illustrated by using parts of a homunculus. The parts from the top of the slice to the bottom along the surface are as follows:

    - Genitalia
    - Toes
    - Foot
    - Leg
    - Hip
    - Trunk
    - Neck
    - Head
    - Shoulder
    - Arm
    - Elbow
    - Forearm
    - Wrist
    - Hand
    - Little finger
    - Ring finger
    - Middle finger

- Index finger
- Thumb
- Eye
- Nose
- Face
- Upper lip
- Lips
- Lower lip
- Teeth, gums, jaw
- Tongue
- Pharynx
- Intra-abdominal

The hand, face, and feet are represented as large structures, and the other parts of the body are represented as smaller structures.
Back to Figure

1. The excitatory area is a small region on the medial side of a monkey's forearm, and the inhibitory area is the entire forearm excluding the excitatory area.
2. In a monkey's palm, the response to different orientations in the decreasing order of response are as follows: Horizonal edge, diagonal edge oriented upward from the left, diagonal edge oriented downward from the left, and vertical edge.
3. Movement is diagonally across the fingertip on a monkey's hand. The amplitude of the responses were higher when the movement was upward to the left than when it was downward to the right.

Back to Figure

1. An arrow points toward dots on the posterior side of the temporal lobe. Red and green dots are in parietal and frontal lobes, and blue dots are in the temporal lobe.
2. A person lies supine.
3. A person reclines on a chair with the knees pulled to the chest.
4. A person, holding a board before them, reclines on a chair with the knees pulled to the chest.

Back to Figure

Both scans locate the anterior cingulate cortex in the anterior part of the brain. The regions of activity are highlighted.

1. The anterior part of the frontal lobe and few parts of temporal lobe and brain stem are highlighted.
2. The anterior and posterior parts of the frontal lobe, some parts of the parietal lobe, and the pons region is highlighted.

Back to Figure

The illustration shows the pain message reaching the periaqueductal gray area in the midbrain. From this area, a signal passes through pons, medulla, and spinal cord to release enkephalin, which causes the pain receptors to reduce the release of substance P, thus reducing the pain message sent to the brain.

Back to Figure

Each set consists of sagittal view and coronal view.

1. The gray matter is lost by a value of 4.5 to 5 in some regions of anterior cingulate cortex and lateral insula, and in few regions of brain stem.
2. The gray matter is gained by a value of 2 to 2.5 in few regions of anterior cingulate cortex and medial insula, and in some regions of brain stem.

Back to Figure

A magnified view of the cross section of the patella shows the Golgi tendon organ. When a hammer taps the organ, signals are sent to the spinal cord through the sensory neuron and cell body. Signals from the spinal cord are sent through the motor neuron to the hamstring muscle, causing the leg to kick backward.

Back to Figure

The parts labeled are as follows:

- Prefrontal cortex in the anterior part of the frontal lobe (Uses information about body and world to select movement and target)
- Premotor cortex in the inferior part of the frontal lobe (Begins programming movement)
- Supplementary motor area in the middle of the frontal lobe (Motor sequences)
- Primary motor cortex (movement execution) in the posterior part of the frontal lobe
- Primary somatosensory cortex in the anterior part of the parietal lobe
- (Body information such as limb positions)
- Posterior parietal cortex in the posterior part of the parietal lobe
- Visual and auditory information in the temporal lobe
- Cerebellum (Modulation and smoothing)

The connections are as follows:

- Between cerebellum and primary motor cortex
- From posterior parietal cortex to visual and auditory information
- From visual and auditory information to prefrontal cortex and premotor cortex
- From prefrontal cortex to premotor cortex and supplementary motor area
- From premotor cortex and supplementary motor area to primary somatosensory cortex
- From primary somatosensory cortex to posterior parietal cortex and primary motor cortex

Back to Figure

The parts are labeled along the cortex and illustrated using parts of a homunculus. The parts from top to bottom are as follows:

- Toes
- Ankle
- Knee
- Hip
- Trunk
- Shoulder
- Elbow
- Wrist
- Hand
- Little finger
- Ring finger
- Middle finger
- Index finger
- Thumb
- Neck
- Brow
- Eyelid and eyeball
- Face
- Lips
- Jaw
- Tongue
- Swallowing

Lips, jaw, and tongue are used for vocalization, jaw and tongue are used for salivation, and tongue is used for mastication.

The hand and face of the homunculus are represented as large structures, and the body, leg, and vocalization organs are represented as smaller structures.
Back to Figure

1. The receptive field extends between the nose and the neck, forming an arc in front of the face.
2. The monkey looks upward. When the arm is out of sight, the angle of the receptive field is between 45 and 90 degrees, when the arm is moved forward, the angle of the receptive field is between negative 20 and 50 degrees, and when the arm is moved across, the angle of the receptive field is between negative 70 and 50 degrees.

Back to Figure

An individual sits at a table. The left hand is hidden from view, and a fake hand is on the table in full view.

1. The index finger of the hidden hand is stroked in synchrony with the index finger of the fake hand.
2. A region of the motor cortex in the brain is highlighted. The individual feels that the sensation is coming from the fake hand.

PART IV COMPLEX BEHAVIOR

Chapter 12. Learning and Memory

Chapter 13. Intelligence and Cognitive Functioning

Chapter 14. Psychological Disorders

Chapter 15. Sleep and Consciousness

12 LEARNING AND MEMORY

© iStockphoto.com/michellegibson

Learning as the Storage of Memories

Amnesia: The Failure of Storage and Retrieval

A Further Look | The Legacy of H. M.

Mechanisms of Consolidation and Retrieval

Where Memories Are Stored

Two Kinds of Learning

Working Memory

Concept Check

Brain Changes in Learning

Long-Term Potentiation

How LTP Happens

Consolidation and Sleep

Changing Our Memories

A Further Look | Total Recall

Concept Check

Learning Deficiencies and Disorders

Effects of Aging on Memory

Alzheimer's Disease

A Further Look | Alzheimer's in a Dish

Other Dementias

Concept Check

In Perspective

Chapter Summary

Study Resources

After reading this chapter, you will be able to

12.1 Explain how the brain is involved in the different types of memory.

12.2 Diagram the neural involvement in processing of information that is stored in memory.

12.3 Describe the changes that occur in the brain as learning proceeds.

12.4 Explain what happens to memories when we sleep.

12.5 Examine how memory changes during aging.

12.6 Contrast the impacts of normal aging and disorders on memory.

At the age of 7, Henry Molaison's life was forever changed by a seemingly minor incident: He was knocked down by a bicycle and was unconscious for 5 minutes. Three years later, he began to have minor seizures, and his first major seizure occurred on his 16th birthday. Still, Henry had a reasonably normal adolescence, taken up with high school, science club, hunting, and roller-skating, except for a 2-year furlough from school because the other boys teased him about his seizures.

After high school, he took a job in a factory, but eventually the seizures made it impossible for him to work. He was averaging 10 small seizures per day and 1 major seizure per week. Because anticonvulsant medications were unable to control the seizures, Henry and his family decided on an experimental operation that held some promise. In 1953, when Henry was 27, a surgeon removed much of both of his temporal lobes, where the seizure activity was originating. The surgery worked, for

the most part: With the help of medication, the petit mal seizures were mild enough not to be disturbing, and major seizures were reduced to about one per year. Henry returned to living with his parents. He helped with household chores, mowed the lawn, and spent his spare time doing difficult crossword puzzles. Later, he worked at a rehabilitation center, doing routine tasks such as mounting cigarette lighters on cardboard store displays.

Henry's problem had nothing to do with his intelligence; it was above average, and his IQ test performance even went up after the operation, probably because he was freed from the interference of the abnormal brain activity. However, there was one important and unexpected effect of the surgery. Although he could recall personal and public events and remember songs from his earlier life, Henry had difficulty learning and retaining new information. He could hold new information in memory for a short while, but if he was distracted or if a few minutes passed, he could no longer recall the information. When he worked at the rehabilitation center, he could not describe the work he did. He did not remember moving into a nursing home in 1980, or even what he had eaten for his most recent meal. And although he watched television news every night, he could not remember the day's news events later or even recall the name of the president (Corkin, 1984; Corkin, Amaral, González, Johnson, & Hyman, 1997; B. Milner, Corkin, & Teuber, 1968).

Henry's inability to form new memories was not absolute. Although he could not find his way back to the new home his family moved to after his surgery if he was more than two or three blocks away, he was able to draw a floor plan of the house, which he had navigated many times daily (Corkin, 2002). Over the years, he became aware of his condition, and he was very insightful about it. In his own words:

> Every day is alone in itself, whatever enjoyment I've had, and whatever sorrow I've had…. Right now, I'm wondering. Have I done or said anything amiss? You see, at this moment everything looks clear to me, but what happened just before? That's what worries me. It's like waking from a dream; I just don't remember. (B. Milner, 1970, p. 37)

Over a period of 55 years, Henry would be the subject of 100 scientific studies that he could not remember; he was known to the world as patient H. M. to protect his privacy. In the next several pages, you will see why many consider H. M.'s surgery the most significant single event in the study of learning.

LEARNING AS THE STORAGE OF MEMORIES

Some one-celled animals "learn" surprisingly well, for example, to avoid swimming toward a light where they have received an electric shock before. We have placed the term *learn* in quotation marks because such simple organisms lack a nervous system; their behavior changes briefly, but if you take a lunch break during your subject's training, when you return, you will have to start all over again. Such a temporary form of learning may help an organism avoid an unsafe area long enough for the danger to pass or linger in a place where food is more abundant. But without the ability to make a permanent record, you could not learn a skill, and experience would not help shape who you are. We will introduce the topic of learning by examining the problem of storage.

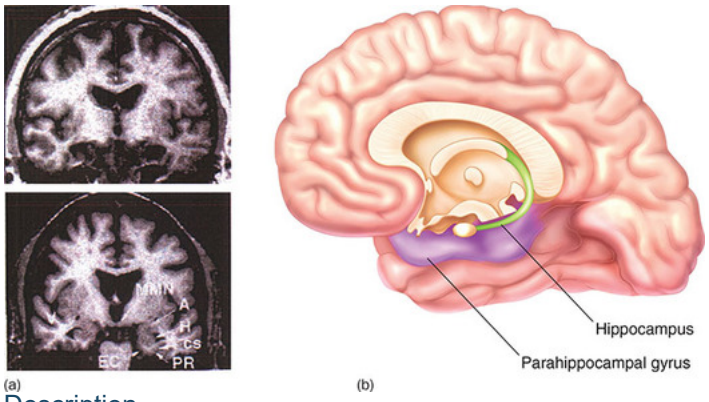
Amnesia: The Failure of Storage and Retrieval

H. M.'s symptoms are referred to as **anterograde amnesia**, an impairment in forming new memories. (*Anterograde* means "moving forward.") This was not H. M.'s only memory deficit; he also experienced **retrograde amnesia**, the inability to remember events prior to impairment. His retrograde amnesia extended from the time of surgery back to about the age of 16; he had a few memories from that period, but he did not

remember the end of World War II or his own graduation, and when he returned for his 35th high school reunion, he recognized none of his classmates. Nevertheless, his memory was better for earlier events than for recent ones; this may seem implausible, but it is typical of patients such as H. M. How far back the retrograde amnesia extends depends on how extensively the medial temporal lobes are damaged and whether the lateral temporal cortex is involved (Bayley, Hopkins, & Squire, 2006; Squire, 2009).

? How does studying amnesia help us understand memory?

H. M.'s surgery damaged or destroyed the hippocampus, nearby structures that along with the hippocampus make up the *hippocampal formation*, and the amygdala. Figure 12.1 shows the location of these structures. Because they are on or near the inside surface of the temporal lobe, they form part of what is known as the medial temporal lobe (remember that *medial* means "toward the middle"). Because H. M.'s surgery was so extensive, it is impossible to tell which structures are responsible for the memory functions that were lost. Studies of patients with varying degrees of temporal lobe damage have helped determine which structures are involved in amnesia and, therefore, in memory. Henry died in 2008 at the age of 82, but he continues to contribute to knowledge about the brain and memory, as A Further Look explains.



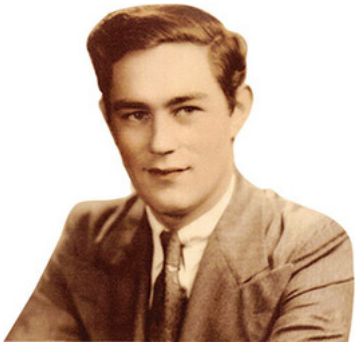
Description

Figure 12.1 Temporal Lobe Structures Involved in Amnesia.
(a) H. M.'s brain (top left) and a normal brain (below). You can see that the amygdala (A), hippocampus (H), and other structures labeled in the normal brain are partly or completely missing in H. M.'s brain. (b) Structures of the medial temporal lobe, which are important in learning. (The frontal lobe is to the left.)

Sources: (a) From "HM's Medial Temporal Lobe Lesion: Findings From Magnetic Resonance Imaging," by S. Corkin, D. G. Amaral, R. G. González, K. A. Johnson, and B. T. Hyman, 1997, *Journal of Neuroscience, 17,* pp. 3964–3979. Copyright © 1997 by the Society for Neuroscience. Used with permission. (b) Adapted with permission from "Remembrance of Things Past," by D. L. Schacter and A. D. Wagner, *Science, 285,* pp. 1503–1504. Illustration: K. Sutliff. © 1999 American Association for the Advancement of Science. Reprinted with permission from AAAS.

A Further Look:

The Legacy of H. M.



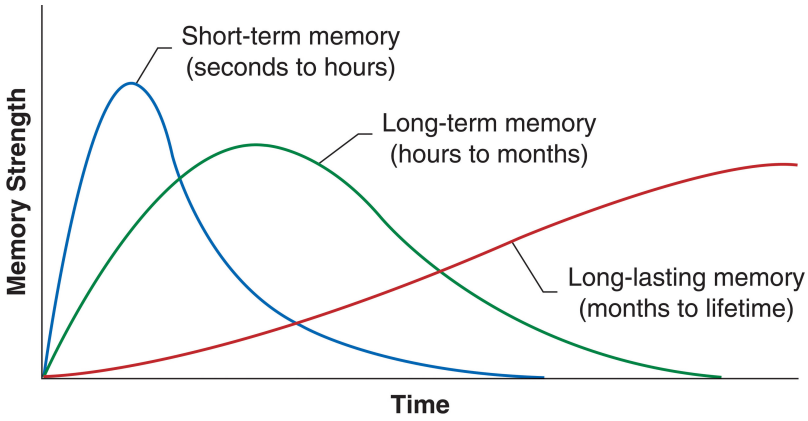
Source: © Wikimedia Commons.

Not only did Henry Molaison devote much of his life to numerous scientific investigations; his brain will continue to be the subject of study for many years to come (Lafee, 2009). Soon after his death, Henry's preserved brain was in a plastic cooler strapped in a seat on a flight from Boston to San Diego; in the next seat was Jacopo Annese, director of the Brain Observatory at the University of California at San Diego. After several months of preparation, Annese and his colleagues dissected Molaison's brain into slices as thin as the width of a hair (70 μm). The 53-hour, uninterrupted procedure was recorded and live-streamed over the web to allow scientific scrutiny and to increase public awareness and engagement (Annese et al., 2014). Each slice of H. M.'s brain was microscopically photographed with such resolution that the data from each *one* would fill 200 DVDs. The data were then combined into a three-dimensional reconstruction of the brain, which is available online. Scientists can navigate through it to the area of their interest and then zoom in to the level of individual neurons. H. M.'s memory problems made him perhaps the most studied subject in neuroscience. Ironically, the man who could not remember will never be forgotten.

The hippocampus consists of several substructures with different functions. The part known as *CA1* provides the primary output from the hippocampus to other brain areas; damage in that part of both hippocampi results in moderate anterograde amnesia and only minimal retrograde amnesia. If the damage includes the rest of the hippocampus, anterograde amnesia is severe. Damage to the entire hippocampal formation results in retrograde amnesia extending back 15 years or more (J. J. Reed & Squire, 1998; Rempel-Clower, Zola, Squire, & Amaral, 1996; Zola-Morgan, Squire, & Amaral, 1986). More extensive retrograde impairment occurs with broader damage or deterioration, like that seen in Alzheimer's disease, Huntington's disease, and Parkinson's disease, apparently because memory storage areas in the cortex are compromised (Squire & Alvarez, 1995).

Mechanisms of Consolidation and Retrieval

H. M.'s memory impairment consisted of two problems: consolidation of new memories and, to a lesser extent, retrieval of older memories. **Consolidation** is the process in which the brain forms a more or less permanent physical representation of a memory. **Retrieval** is the process of accessing stored memories—in other words, the act of remembering. When a rat presses a lever to receive a food pellet, or a child is bitten by a dog, or you skim through the headings in this chapter, the experience is held in memory at least for a brief time. But just like the phone number that is forgotten when you don't reach your party the first time you dial, an experience does not necessarily become a permanent memory; if it does, the transition takes time. Until the memory is consolidated, it is particularly fragile. New memories may be disrupted just by engaging in another activity, and even older memories are vulnerable to intense experiences such as emotional trauma or electroconvulsive shock treatment (a means of inducing convulsions, usually in treating depression). Researchers divide memory into two stages, *short-term memory* and *long-term memory*. Long-term memory, at least for some kinds of learning, can be divided into two stages that have different durations and occur in different locations (Figure 12.2), as we will see later (McGaugh, 2000).



Description

Figure 12.2 Stages of Consolidation.
Making a memory permanent involves multiple stages and different processes.

Source: Reprinted with permission from "Memory—A Century of Consolidation," by J. L. McGaugh, *Science, 287,* pp. 248–251. Copyright 2000 American Association for the Advancement of Science.

An animal study clearly demonstrates that the hippocampus participates in consolidation. Rats were trained in a water maze, a tank of murky water from which they could escape quickly by learning the location of a platform submerged just under the water's surface (Figure 12.3; Riedel et al., 1999). Then, for 7 days, the rats' hippocampi were temporarily disabled by a drug that blocks receptors for the neurotransmitter glutamate. Eleven days later—plenty of time for the drug to clear the rats' systems—they performed poorly compared with control subjects (Riedel et al., 1999). Researchers have been able to "watch" the consolidation happening in humans, using brain scans and event-related potentials. Presenting words or pictures activated the hippocampus and adjacent cortex; how well the material was remembered later could be predicted from how much activation occurred in those areas during stimulus presentation (Figure 12.4; Alkire, Haier, Fallon, & Cahill, 1998; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; G. Fernández et al., 1999).

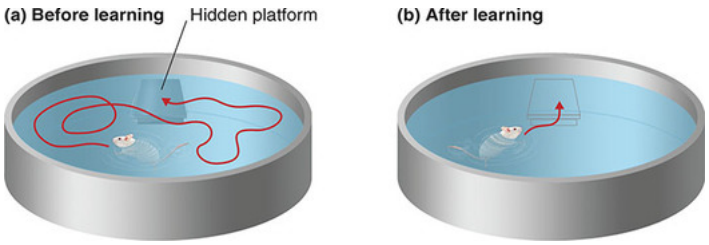
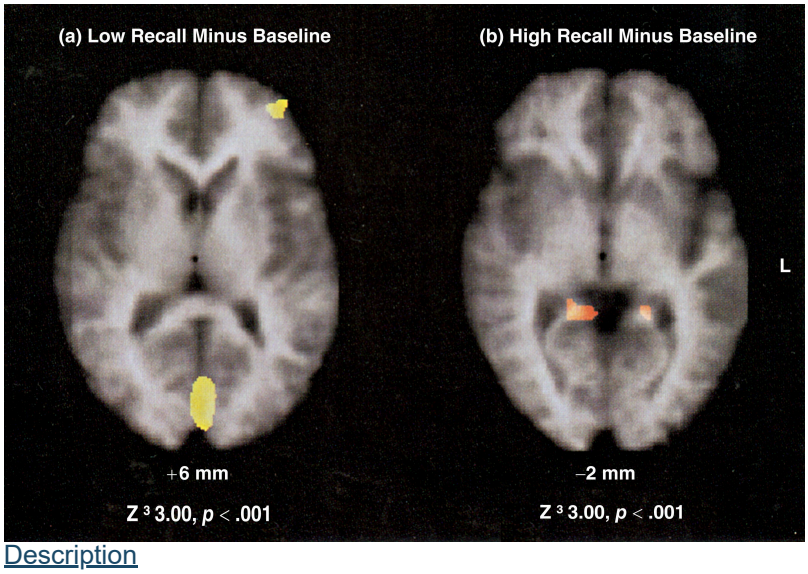


Figure 12.3 A Water Maze.
The rat learns to escape the murky water by finding the platform hidden just below the surface.

Figure 12.4 Hippocampal Activity Related to Consolidation.
The arrow is pointing to the hippocampal region. Reds and yellows indicate positive correlations of activity at the time of learning with later recall; blues indicate negative correlations.

Source: From "PET Imaging of Conscious and Unconscious Memory," by M. T. Alkire, R. J. Haier, J. H. Fallon, and S. J. Barker, 1996, *Journal of Consciousness Studies, 3,* pp. 448–462.

Animals that were given the glutamate-blocking drug at the time of testing instead of immediately after training also had impaired recall in the water maze, indicating that the hippocampus has a role in retrieval as well as consolidation. Researchers have used PET scans to confirm that the hippocampus also retrieves memories in humans (Schacter, Alpert, Savage, Rauch, & Albert, 1996; Squire et al., 1992). Figure 12.5 shows increased activity in the hippocampi while the research participants recalled words learned during an experiment. The involvement of the hippocampus in retrieval seems inconsistent with H. M.'s ability to recall earlier memories. But the memories that patients with hippocampal damage can recall are of events that occurred at least 2 years before their brain damage. Many researchers have concluded that the hippocampal mechanism plays a time-limited role in consolidation and retrieval, a point we will examine shortly. This diminishing role of the hippocampus would explain why older memories suffer less than recent memories after hippocampal damage.



Description

Figure 12.5 Hippocampal Activity in the Human Brain During Retrieval.
(a) As participants tried to recall visually presented words that had been poorly

learned (35% recall rate), the prefrontal and visual areas, but not the hippocampi, were highly activated compared with the baseline condition. (b) However, the successful recall of well-learned words (79% recall rate) activated both hippocampal areas.

Source: Reprinted with permission from "Conscious Recollection and the Human Hippocampal Formation: Evidence From Positron Emission Tomography," by D. L. Schacter et al., *Proceedings of the National Academy of Sciences, USA, 93,* pp. 321–325. Copyright 1996 National Academy of Sciences, USA.

The prefrontal area is also active during learning and retrieval, and some researchers think that it directs the search strategy required for retrieval (Buckner & Koutstaal, 1998). Indeed, the prefrontal area is active during effortful attempts at retrieval, whereas the hippocampus is activated during successful retrieval (see Figure 12.5; Schacter et al., 1996). We will look at the role of the frontal area again when we consider working memory and Korsakoff syndrome.

We saw in Chapter 5 that rewards such as drugs increase activity in dopamine neurons. Because reward plays a crucial role in learning, we might suspect that dopamine has some function in learning, and that is indeed the case. Blocking dopamine receptors in guinea pigs shortly after learning impairs consolidation and memory (K.-N. Lee & Chirwa, 2015), and increasing dopamine levels by injecting the dopamine precursor levodopa improves memory in humans (Chowdhury, Guitart-Masip, Bunzeck, Dolan, & Düzel, 2012). Novel experience, such as exploring an unfamiliar environment, increases dopamine activity; placing rats in a novel environment either before or after learning improves learning (S.-H. Wang, Redondo, & Morris, 2010). In humans, learning can be increased by dopamine-enhancing stimulation as simple as viewing novel photographs from *National Geographic* (Fenker, Frey, Schuetze, & Heipertz, 2008).

The reason dopamine-enhancing stimulation enhances learning, whether it occurs before or after the learning experience, is because dopamine affects consolidation of long-term memory, rather than improving short-term memory (Lisman, Grace, & Duzel, 2011). Dopamine release initiates the synthesis of proteins in the postsynaptic neuron. These plasticity-related proteins are necessary for consolidation to occur, as we will see later, and drugs that block their synthesis inhibit learning (Clopath, 2012).

Dopamine does not signal rewards so much as it signals *errors in prediction*. Firing increases in dopamine neurons only if the reward is unexpected—either of greater value than usual or occurring when it has been infrequent (Schultz, 2016). If the reward is expected, the firing rate remains the same, and it declines if the reward is less than expected. In other words, evolution has tailored learning specifically to help us cope with changes in our environment and in our circumstances.

Where Memories Are Stored

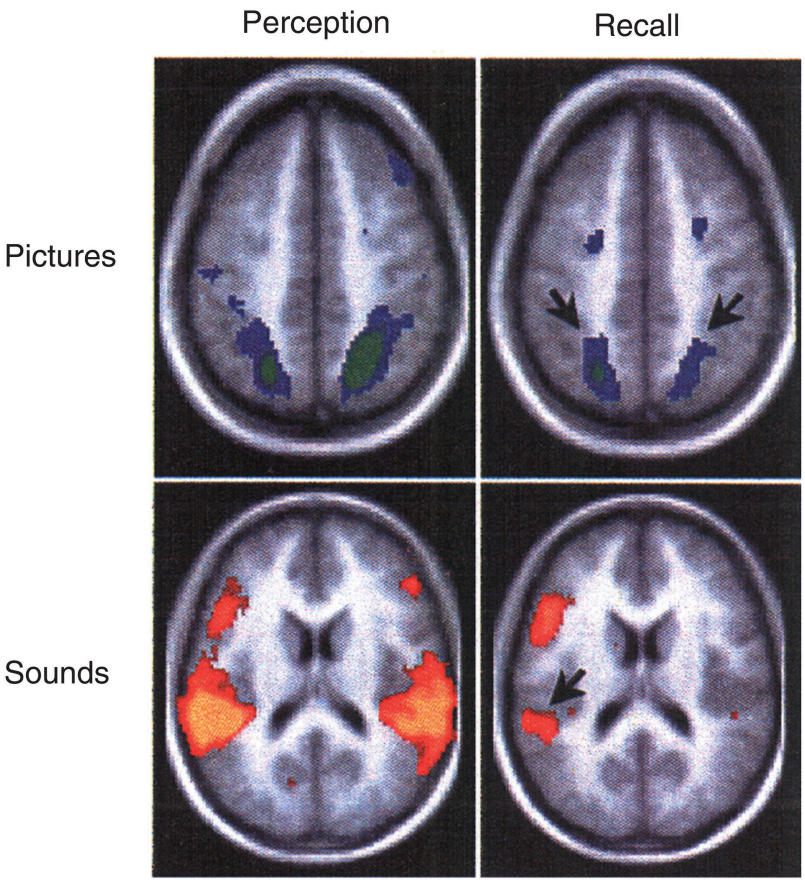
The hippocampal area is not the permanent storage site for memories. If it were, patients like H. M. would not remember anything that happened before their damage occurred. According to most researchers, the hippocampus stores information temporarily in the hippocampal formation; then, over time, a more permanent memory is consolidated elsewhere in the brain. A study of mice that had learned a spatial discrimination task supported the hypothesis: Over 25 days of retention testing, metabolic activity progressively decreased in the hippocampus and increased in the cortical areas (Bontempi, Laurent-Demir, Destrade, & Jaffard, 1999). Although completing this transition takes time, the memory is represented in prefrontal cortex (PFC) cells quickly (Kitamura et al., 2017). Fear conditioning in mice activated specific cells in the hippocampus and the PFC. The next day, placing the mice back in the chamber in which they had received shock activated those cells in the hippocampus but not in the PFC. However, stimulating cells in either location elicited the learned fear response ("freezing"), indicating that the PFC cells already held a "silent" memory. Two weeks later, the PFC cells had developed increased synaptic connections, and the hippocampal cells had lost connections; when the mice were placed in the chamber, the PFC cells became active and mice froze, but the

hippocampal cells remained silent, indicating that responsibility for the memory had been transferred to the PFC.

This progression apparently takes longer in humans. Christine Smith and Larry Squire (2009) used fMRI to image the brain's activity while human volunteers recalled news events from the past 30 years. Activity in the hippocampus was greatest as they recalled recent events, declined as they recalled events as far back as 12 years, and remained stable after that. Beyond the hippocampus—in the prefrontal, temporal, and parietal cortex—activity increased progressively with increasing age of the memory. So your brain works rather like your computer when it transfers volatile memory from RAM to the hard drive—it just takes longer.

? Is there a place where memories are stored?

In Chapter 3, you learned that when Wilder Penfield (1955) stimulated association areas in the temporal lobes of surgery patients, he often evoked visual and auditory experiences that seemed like memories. We speculated that memories might be stored there, and more recent research has supported that idea, with memories for sounds activating auditory areas and memories for pictures evoking activity in the occipital region (Figure 12.6; M. E. Wheeler, Petersen, & Buckner, 2000). You also saw in Chapter 9 that when we learn a new language, it is stored near Broca's area, and naming tools activates the premotor cortex. Naming colors activates temporal lobe areas near where we perceive color (A. Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995), and spatial memories appear to be stored in the parietal area and verbal memories in the left frontal lobe (F. Rösler, Heil, & Henninghausen, 1995). Thus, all memories are not stored in a single area, nor is each memory distributed throughout the brain. Rather, different memories are in different cortical areas, apparently according to where the information they are based on was processed.



Description

Figure 12.6 Functional MRI Scans of Brains During Perception and Recall. Memories of pictures and sounds evoked responses in the same general areas (arrows) as the original stimuli.

Source: From "Memory's Echo: Vivid Remembering Reactivates Sensory-Specific Cortex," by M. E. Wheeler et al., *Proceedings of the National Academy of Sciences, USA, 97,* pp. 11125–11129, fig. 1c, d, e, f, p. 11127. © 2000 National Academy of Sciences, USA.

An interesting example is the type of cells involved in place memory. **Place cells**, which increase their rate of firing when the individual is in a specific location in the environment, are found in the hippocampus. Each cell has a place field (overlapping somewhat with others), and together these cells form a map of the environment. This map develops during the first few minutes of exploration; the cells' fields are then remapped when entering a new environment, but they are restored when returning to the original location (Figure 12.7; Guzowski, Knierim, & Moser, 2004; M. A. Wilson & McNaughton, 1993). The fields are dependent on spatial cues in the environment, including visual, tactile, and even olfactory cues (M. L. Shapiro, Tanila, & Eichenbaum, 1997). Place cells do more than indicate an individual's current location. For example, they contribute the context of location that is so important in memories of events (D. M. Smith & Mizumori, 2006). They also provide spatial memory required for planning navigation; as rats paused at choice points in a maze with which they were well experienced, cells with place fields in the alternative sections fired in sequence, as if the rats were simulating the two choices (A. Johnson & Redish, 2007). Functional MRI has confirmed that humans have place cells; their activity is so precise that the investigators could determine the subject's "location" in a computer-generated virtual environment (Hassabis et al., 2009).

Figure 12.7 Recordings From Place Cells in a Rat in a Circular Runway. The recordings are from seven different place cells, indicated by different colors. Note that each cell responds when the rat is in a particular part of the runway. (Due to cue similarities in a circular apparatus, cells occasionally respond on the opposite side of the circle.)

Source: Reprinted by permission from Macmillan Publishers Ltd. From "Neural Plasticity in the Ageing Brain," by S. N. Burke and C. A. Barnes, 2006, *Nature Reviews Neuroscience, 7,* pp. 30–40. Nature Publishing Group.

Two Kinds of Learning

Learning researchers were in for a revelation when they discovered that H. M. could readily learn some kinds of tasks (Corkin, 1984). One was mirror drawing, in which the individual uses a pencil to trace a path around a pattern, relying solely on a view of the work surface in a mirror. H. M. improved in mirror-drawing ability over 3 days of training, and he learned to solve the Tower of Hanoi problem (Figure 12.8). But he could not remember learning either task, and on each day of practice, he denied even having seen the Tower puzzle before (N. J. Cohen, Eichenbaum, Deacedo, & Corkin, 1985; Corkin, 1984). What this means, researchers realized, is that there are two categories of memory processing. **Declarative memory** involves learning that results in memories of facts, people, and events that a person can verbalize or declare. For

example, you can remember being in class today, where you sat, who was there, and what was discussed. Declarative memory includes a variety of subtypes, such as *episodic memory* (events), *semantic memory* (facts), *autobiographical memory* (information about oneself), and *spatial memory* (the location of the individual and of objects in space). **Nondeclarative memory** involves memories for behaviors; these memories result from procedural or skills learning, emotional learning, and stimulus-response conditioning. Learning mirror tracing or how to ride a bicycle or solve the Tower of Hanoi problem are examples of nondeclarative learning or, more specifically, procedural or skills learning; remembering practicing the tasks involves declarative learning. Another way of putting it, which is admittedly a bit oversimplified, is that declarative memory is informational, while nondeclarative memory is more concerned with the control of behavior. Just as we have *what* and *where* pathways in vision and audition, we have a *what* and a *how* in memory.

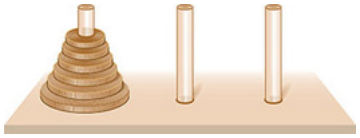


Figure 12.8 The Tower of Hanoi Problem.
The task is to relocate the rings in order onto another post by moving them one at a time and without ever placing a larger ring over a smaller one.

? What are the two kinds of learning?

The main reason to distinguish between the two types of learning is that they have different origins in the brain; studying them can tell us something about how the brain carries out its tasks. For years, it looked like we were limited to studying the distinction in the rare human who had brain damage in just the right place; hippocampal lesions did not seem to affect learning in rats, so researchers thought that rats did not have an equivalent of declarative memory. But it just took selecting the right tasks. R. J. McDonald and White (1993) used an apparatus called the radial arm maze, a central platform with several arms radiating from it (Figure 12.9). Rats with damage to both hippocampi could learn the simple conditioning task of going into any lighted arm for food. But if every arm was baited with food, the rats could not remember which arms they had visited and repeatedly returned to arms where the food had already been eaten.

Figure 12.9 A Radial Arm Maze.
The rat learns where to find food in the maze's arms. The arms are often enclosed by walls.

Source: Mauro Fermariello/Science Source.

Conversely, rats with damage to the striatum could remember which arms they had visited but could not learn to enter lighted arms. Because Parkinson's disease and Huntington's disease damage the basal ganglia (which include the striatum), people with these disorders have trouble learning procedural tasks, such as mirror tracing or the Tower of Hanoi problem (Gabrieli, 1998). Incidentally, the term *declarative* seems inappropriate with rats; researchers have often preferred the term *relational memory*, which implies that the individual must learn relationships among cues, an idea that applies equally well to humans and animals.

You already know that the amygdala is important in emotional behavior, but it also has a significant role in nondeclarative emotional learning. Bechara and his colleagues (1995) studied a patient with damage to both amygdalas and another with damage to both hippocampi. The researchers attempted to condition an emotional response in the patients by sounding a loud boat horn when a blue slide was presented but not when the slide was another color. The patient with amygdala damage reacted emotionally to the loud noise, as indicated by increased skin conductance responses (see Chapter 8). He could also tell the researchers which slide was followed by the loud noise, but the blue slide never evoked a skin conductance increase; in other words, conditioning was absent. The patient with hippocampal damage showed an emotional response and conditioning, but he could not tell the researchers which color the loud sound was paired with. This neural distinction between declarative learning and nondeclarative emotional learning may well explain how an emotional experience can have a long-lasting effect on a person's behavior even when the person does not remember the experience.

The amygdala has an additional function that cuts across learning types. Both positive and negative emotions enhance the memorability of any event; the amygdala strengthens even declarative memories about emotional events, apparently by increasing activity in the hippocampus. Electrical stimulation of the amygdala activates the hippocampus, and it enhances learning of a non-emotional task, such as a choice maze (McGaugh, Cahill, & Roozendaal, 1996). In humans, memory for both pleasant and aversive emotional material is related to the amount of activity in both amygdalas while viewing the material (Cahill et al., 1996; Hamann, Ely, Grafton, & Kilts, 1999).

Working Memory

The brain stores a tremendous amount of information, but information that is merely stored is useless. It must be available, not just when it is being recalled into awareness but when the brain needs it for carrying out a task. **Working memory** provides a temporary "register" for information while it is being used. Working memory holds a password you just looked up long enough for you to type it in; it also holds information retrieved from long-term memory while it is integrated with other information for use in problem solving and decision making. Without working memory, we could not do long division, plan a chess move, or even carry on a conversation.

? Why is working memory important?

Think of working memory as like the RAM in your computer. The RAM holds information temporarily while it is being processed or used, but the information is stored elsewhere on the hard drive. But we should not take any analogy too far. Working memory has a very limited capacity (with no upgrades available), and information in working memory fades within seconds. So if you make a mistake entering the password you just looked up, you'll probably have to look it up again.

The *delayed match-to-sample task* described in Chapter 11 provides an excellent means of studying working memory. During the delay period, cells remain active in

one or more of the association areas in the temporal and parietal lobes, depending on the nature of the stimulus (Constantinidis & Steinmetz, 1996; Fuster & Jervey, 1981; Miyashita & Chang, 1988). Cells in these areas apparently help maintain the memory of the stimulus, but they are not the location of working memory. If a distracting stimulus is introduced during the delay period, the altered firing in these locations ceases abruptly, but the animals are still able to make the correct choice (Constantinidis & Steinmetz, 1996; E. K. Miller, Erickson, & Desimone, 1996). Cells in the prefrontal cortex have several attributes that make them better candidates as working memory specialists. Not only do they increase firing during a delay; they also maintain the increase despite a distracting stimulus (E. K. Miller et al., 1996). Some respond selectively to the correct stimulus (di Pellegrino & Wise, 1993; E. K. Miller et al., 1996). Others respond to the correct stimulus only if it is presented in a specific position in the visual field; they apparently integrate information from cells that respond only to the stimulus with information from cells that respond to the location (S. C. Rao, Rainer, & Miller, 1997). Prefrontal damage impairs humans' ability to remember a stimulus during a delay (D'Esposito & Postle, 1999). All these findings suggest that the prefrontal area plays the major role in working memory.

Although the prefrontal cortex serves as a temporary memory register, its function is apparently more than that of a neural blackboard. In Chapters 3 and 8, you learned that damage to the frontal lobes impairs a person's ability to govern his or her behavior in several ways. Many researchers believe that the primary role of the prefrontal cortex in learning is as a central executive. That is, it manages certain kinds of behavioral strategies and decision making and coordinates activity in the brain areas involved in the perception and response functions of a task, all the while directing the neural traffic in working memory (Wickelgren, 1997).

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- What determines the symptoms and the severity of symptoms of amnesia?
- Describe the two kinds of learning and the related brain structures.
- Working memory contributes to learning and to other functions. How?

BRAIN CHANGES IN LEARNING

Learning is a form of neural plasticity that changes behavior by remodeling neural connections. Specialized neural mechanisms have evolved to make the most of this capability. We will look at them in the context of long-term potentiation.

? How do neurons change during learning?

Long-Term Potentiation

Almost a century ago, Donald Hebb (1940) stated what has become known as the **Hebb rule**: If an axon of a presynaptic neuron is active while the postsynaptic neuron is firing, the synapse between them will be strengthened. We saw this principle in action during the development of the nervous system, when synaptic strengthening helped determine which neurons would survive; some of that plasticity is retained in the mature individual. Researchers have long believed that to understand learning as a physiological process, they would have to figure out what happens at the level of the neuron and particularly at the synapse.

Long-term potentiation (LTP) is a persistent strengthening of synapses that results from the simultaneous activation of presynaptic neurons and postsynaptic neurons (Cooke & Bliss, 2006). LTP can be induced in the laboratory by stimulating both

neurons at the same time or by stimulating the presynaptic neuron adequately to cause the postsynaptic neuron to fire. As you can see in Figure 12.10a, the postsynaptic neuron's response to a test stimulus is much stronger following induction of LTP. What is remarkable about LTP is that it can last for hours in tissue cultures and months in laboratory animals (Cooke & Bliss, 2006). LTP has been studied mostly in the hippocampus, but it also occurs in several other areas, including the visual, auditory, and motor cortex. So LTP appears to be a characteristic of much of neural tissue, at least in the areas most likely to be involved in learning.

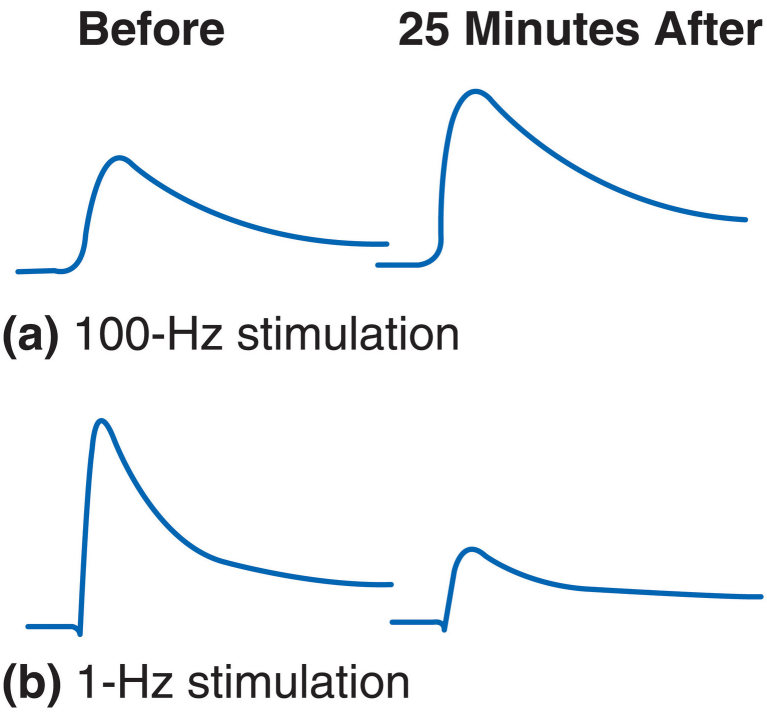


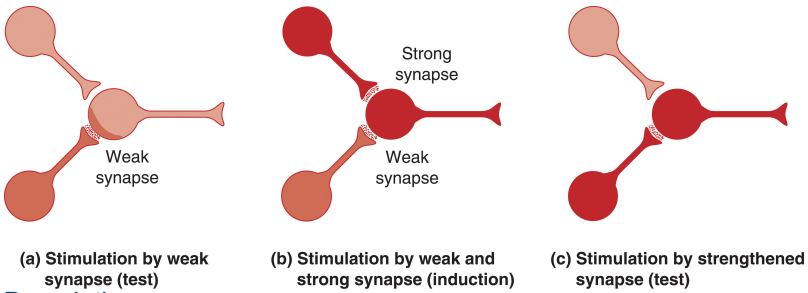
Figure 12.10 LTP and LTD in the Human Brain.
The graphs show excitatory postsynaptic potentials in response to a test stimulus before and after repeated stimulation. (a) 100-hertz (Hz) stimulation produced LTP. (b) 1-Hz stimulation produced LTD, which blocked the potentiation established earlier.

Source: From "Long-Term Modifications of Synaptic Efficacy in the Human Inferior and Middle Temporal Cortex," by W. R. Chen et al., *Proceedings of the National Academy of Sciences, USA, 93,* pp. 8011–8015. Copyright 1996 National Academy of Sciences, USA. Used with permission.

Neural functioning requires weakening synapses as well as strengthening them. **Long-term depression (LTD)** is a decrease in the strength of synapses that occurs when stimulation of presynaptic neurons is insufficient to activate the postsynaptic neurons (Cooke & Bliss, 2006). Potentiation can be depressed in a postsynaptic neuron by applying a low-frequency pulse to the presynaptic neuron for a few minutes, causing the presynaptic neuron to fire but not the postsynaptic neuron (Figure 12.10b). LTD is believed to be the mechanism the brain uses to modify memories and to clear old memories to make room for new information (Stickgold, Hobson, Fosse, & Fosse, 2001).

Activity in presynaptic neurons also influences the sensitivity of nearby synapses. If a weak synapse and a strong synapse on the same postsynaptic neuron are active simultaneously, the weak synapse will be potentiated; this effect is called **associative long-term potentiation** (Figure 12.11). Associative LTP is usually studied in isolated brain tissue with artificially created weak and strong synapses, but it has important behavioral implications, which is why it interests us. Electric shock evokes a strong response in the lateral amygdala, where fear is registered, while an auditory stimulus produces only a minimal response there. Rogan, Stäubli, and LeDoux (1997)

repeatedly paired a tone with shock to the feet of rats. Because of this procedure, the tone alone began to evoke a significantly increased response in the amygdala, as well as an emotional “freezing” response in the rats. You may recognize this scenario as an example of *classical conditioning*; we could easily change the labels in Figure 12.11 from “Strong synapse” to “Electric shock” and from “Weak synapse” to “Auditory tone.” Researchers believe that associative LTP is the basis of classical conditioning, and Rogan and colleagues’ results support that view. LTP, LTD, and associative LTP can all be summed up in this expression: “Cells that fire together wire together.”

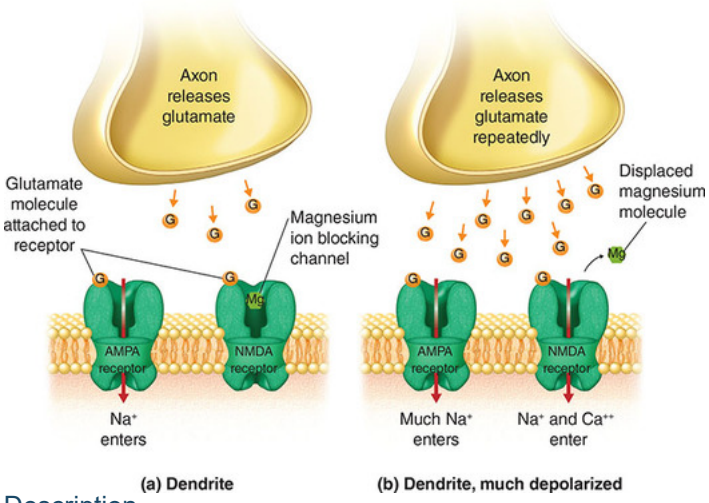


Description

Figure 12.11 Associative LTP.
(a) Initially, the weak synapse produces only a very small excitatory postsynaptic potential. (b) Simultaneous activation of a strong synapse along with activity in the weak synapse induces associative LTP. (c) Following associate LTP, the much larger excitatory postsynaptic potential indicates that the weak synapse has been potentiated.

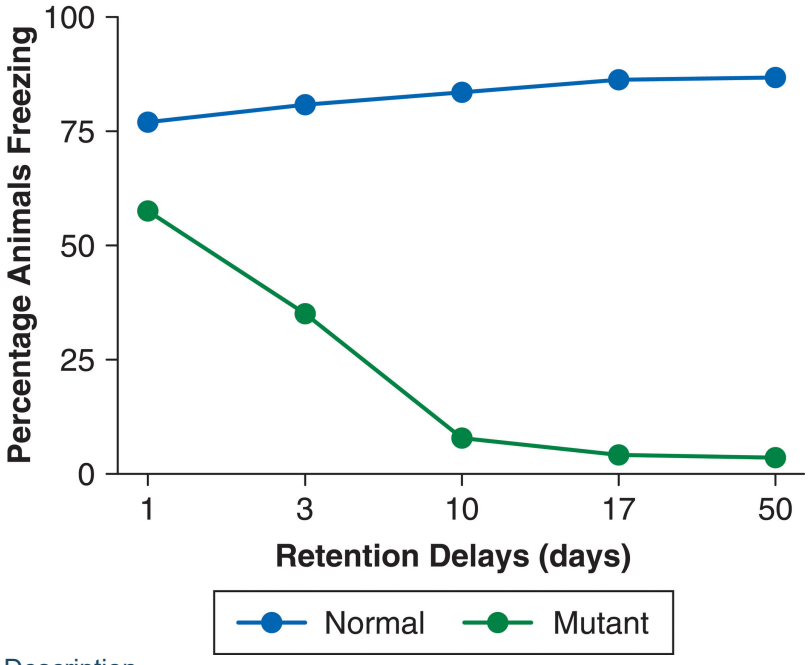
How LTP Happens

LTP has been studied most often in the neurons connecting CA1 and CA3 of the hippocampus, and we will use those findings as our model here without going into the variations that occur in other areas of the brain. LTP is induced through a cascade of events at the synapse. In CA1 (and in most locations), the neurotransmitter involved is glutamate, which is detected by two types of receptors: the AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor and the NMDA (N-methyl-d-aspartate) receptor. Initially, glutamate activates AMPA receptors but not NMDA receptors, because they are blocked by magnesium ions (Figure 12.12). During LTP induction, activation of the AMPA receptors by the first few pulses of stimulation partially depolarizes the membrane, and this dislodges the magnesium ions. The resulting large influx of calcium ions activates a host of *protein kinases*, enzymes that alter or activate other proteins (Lüscher & Malenka, 2012). One of the protein kinases, CaMKII (calcium/calmodulin-dependent kinase II), is required for LTP. Mice with two mutant, nonfunctioning genes for the alpha form of CaMKII fail to show LTP; those with one mutant and one functioning gene do show LTP, but it is not consolidated into long-term memory (Figure 12.13; Frankland, O’Brien, Ohno, Kirkwood, & Silva, 2001). Several plasticity-related genes are activated as well (Kelleher, Govindarajan, & Tonegawa, 2004); they, along with newly activated proteins, begin producing structural changes in the synapse (Lüscher & Malenka, 2012).



Description

Figure 12.12 Participation of Glutamate Receptors in LTP.
(a) Initially, glutamate activates the AMPA receptors but not the NMDA receptors, which are blocked by magnesium ions. (b) However, if the activation is strong enough to partially depolarize the postsynaptic membrane, the magnesium ions are ejected. The NMDA receptor can then be activated, allowing sodium and calcium ions to enter.



Description

Figure 12.13 Retention in Normal and αCaMKII-Deficient Mice Over Time.
Mice given foot shocks in a conditioning chamber were later tested for memory of the foot shocks by observing emotional "freezing" when they were returned to the chamber. Note that in the mice heterozygous for the mutant gene, memory had begun to decay after 3 days and they failed to form permanent memory.

Source: "CaMKII-Dependent Plasticity in the Cortex Is Required for Permanent Memory," by P. W. Frankland, C. O'Brien, M. Ohno, A. Kirkwood, & A. J. Silva, 2001, Nature, 411, pp. 309–313. Figure 1.

Within 45 to 60 minutes after LTP, postsynaptic neurons develop dramatically increased numbers of **dendritic spines**, outgrowths from the dendrites that partially bridge the synaptic cleft and make the synapse more sensitive (Figure 12.14; N. Toni, Buchs, Nikonenko, Bron, & Muller, 1999). Existing spines also enlarge or split down the middle to form two spines (Matsuzaki, Honkura, Ellis-Davies, & Kasai, 2004). Another important structural change is the appearance of new AMPA receptors, which increase synaptic strength (Lüscher & Malenka, 2012). These come from a pool of silent receptors that are transported into the spines from within the dendrite; they can recycle between the cytoplasm and the membrane or in the other direction within mere tens of minutes. A further change that occurs in support of learning is the generation of new neurons in the hippocampus; though the rate of neurogenesis is relatively low in adults, over the life span, new neurons add up to an estimated 10% to 20% of the population (Jacobs, van Praag, & Gage, 2000). Numerous studies show that learning is impaired by blocking neurogenesis and enhanced by increasing new cell birth. New neurons are more active than mature ones, have a lower threshold for LTP induction, and are better at making fine discriminations, such as distinguishing between the contexts in which reward occurs and does not occur (Yau, Li, & So, 2015). It also appears that the new neurons interfere with established LTP in the hippocampus, clearing the way for new memories and aiding the transfer of memory to the cortex (Kitamura & Inokuchi, 2014).

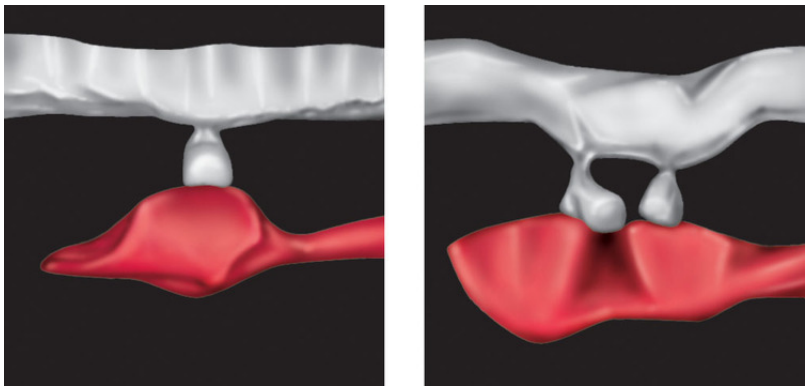


Figure 12.14 Increase in Dendritic Spines Following LTP.
(a) A single synaptic spine on a dendrite (white) and a presynaptic terminal (red). (b) The same spine split into two following LTP.

Source: Adapted from "LTP Promotes Formation of Multiple Spine Synapses Between a Single Axon Terminal and a Dendrite," by N. Toni et al., Nature, 402(6706), pp. 421–425.

? How does the brain grow during learning?

? How do the roles of the hippocampus and the cortex differ?

With all that growth, you might suspect that there would be some increase in the volume of the brain areas that are involved in LTP. In fact, this does happen to some extent. London taxi drivers, who are noted for their ability to navigate the city's complex streets entirely from memory, spend about 2 years learning the routes before they can be licensed to operate a cab. Maguire and her colleagues (2000) used MRI to scan the brains of 16 drivers. The posterior part of their hippocampi, known to be involved in spatial navigation, was larger than in males of similar age. (Overall hippocampal volume did not change; their anterior hippocampi were smaller.) The difference was greater for cabbies who had been driving for the longest time, which we would expect if the difference was due to experience.

Consolidation and Sleep

The hippocampus can acquire learning "on the fly" while the event is in progress, but a longer time is needed for long-term storage of declarative memories in the cortex.

Many researchers now believe that the hippocampus transfers information to the cortex during times when the hippocampus is less occupied, even during sleep (Lisman & Morris, 2001; McClelland, McNaughton, & O'Reilly, 1995). During sleep, neurons in rats' hippocampus and cortical areas repeat the pattern of firing that occurred during learning (Louie & Wilson, 2001; Y.-L. Qin, McNaughton, Skaggs, & Barnes, 1997). Human EEG and PET studies showed the hippocampus repeatedly activating the cortical areas that participated in the daytime learning, and this reactivation was accompanied by significant task improvement the next morning without further practice (Figure 12.15; Maquet et al., 2000; Wierzynski, Lubenov, Gu, & Siapas, 2009). Even a daytime nap is enough to evoke this kind of activity in the hippocampus and improve subsequent performance (Studte, Bridger, & Mecklinger, 2015). Anne Schapiro and her colleagues (2018) collected fMRI data while their volunteers reviewed the images they had just learned, then kept the scanner running as they napped; comparing the data showed that images that had been remembered less well during the post-training test were singled out for extra replay, which resulted in improved recall later. Presumably, "offline" replay provides the cortex with the opportunity to undergo LTP at the more leisurely pace it requires (Lisman & Morris, 2001). During sleep, more than 100 genes increase their activity, and many of those have been identified as major players in protein synthesis, synaptic modification, and memory consolidation (Cirelli, Gutierrez, & Tononi, 2004).

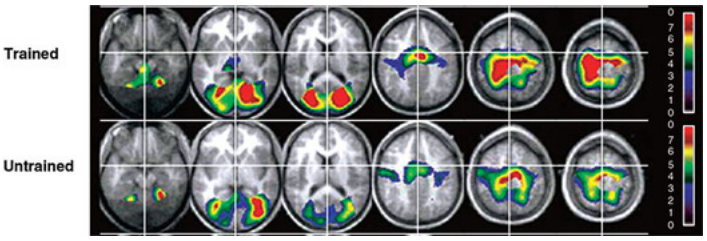


Figure 12.15 PET Scans of Brain Activity During Sleep Following Learning. Areas previously active during learning are also more active during sleep in the trained subjects, but not in the untrained subjects.

Source: Reprinted by permission from Macmillan Publishers Ltd. From "Experience-Dependent Changes in Cerebral Activation During Human REM Sleep," by P. Maquet et al., 2000, *Nature Neuroscience, 3,* pp. 831–855, fig. 2, p. 833. Nature Publishing Group.

Changing Our Memories

As hard as the brain works to make memories "permanent," it is still important that these records not be inscribed in stone. Things change; the waterhole we learned was reliable over several visits is now becoming progressively more stagnant, so we must range in other directions until we find a new source of water. And sometimes erroneous learning must be corrected; the first two redheads we knew were hot tempered, and it will take meeting additional redheads to change what we have learned. A memory needs to be stable to be useful, but at the same time it must remain malleable; there are several ways the brain accomplishes this.

Extinction

The first is *extinction*. The experimenter sounds a tone just before delivering a puff of air to your eye; after only a few trials, you blink just because you hear the tone. This doesn't happen simply because you understand that the air blast is coming; it occurs more quickly than you can make a voluntary response. Then the experimenter sounds the tone several times without administering the puff of air. Slowly, the tone loses its power to make you blink. The memory is not gone; if the experimenter repeats the puff of air, you will be back to blinking every time you hear the tone. Nor is this an example of forgetting. Rather, extinction involves new learning; one indication

is that, like LTP, extinction requires activation of NMDA receptors, and blocking these receptors eliminates extinction (Santini, Muller, & Quirk, 2001).

Forgetting

Most memories dissipate at least somewhat over time if they are not used regularly. We usually think of forgetting as a defect, but it can also be useful. The brain actively removes useless information to prevent the saturation of synapses with information that is not called up regularly or has not made connections with other stored memories. One way this *active forgetting* occurs involves an unexpected effect of dopamine. During learning, some dopaminergic neurons facilitate learning while, simultaneously, another subset causes the memory-modified neurons to release a cascade of proteins that reduce the size and density of the postsynaptic dendrites (R. L. Davis & Zhong, 2017). This effect drops off shortly after learning occurs, which suggests that its role is to erase memories that don't receive further reinforcement (R. L. Davis & Zhong, 2017; Shuai et al., 2010). In addition, certain neurons in the hypothalamus (melanin concentrating hormone neurons, MCH) inhibit activity in hippocampal neurons. Stimulating these neurons had no effect on learning, but it interfered with memory if administered later, suggesting a role in forgetting (Izawa et al., 2019). MCH neurons are most active during rapid eye movement sleep, a stage of sleep during which dreaming occurs and unneeded memories are removed.

Efficient memory involves a balance between remembering and forgetting. Later in this chapter, we will see how devastating memory impairment can be. A Further Look shows that there is another side to the coin as well.

A Further Look:

Total Recall

Source: © iStockphoto.com/michellegibson

Most of us would like to remember more and forget less. But Jill Price wrote to neuropsychologist James McGaugh at the University of California, Irvine, asking for help because she couldn't forget; she could remember what she did and what was happening in the world for practically every day of her life, and she was often tormented by bad memories (J. Marshall, 2008; E. S. Parker, Cahill, & McGaugh, 2006). Two years later, two men with similar memory capabilities came forward, but unlike Price, Brad Williams and Rick Baron could keep their memories at bay (Elias, 2008; D. S. Martin, 2008). Williams used his memory in his work as a radio news

reporter; Baron was unemployed but supported himself in part by winning contests that utilize his memory for facts. The researchers were eager to understand what fuels this unusual ability because the knowledge could help the memory impaired.

These total recallers did no better than controls when they were asked to recall personal events from a particular day during the past week, such as what they ate for breakfast and what they did during the day. But their memories from the month before were almost as good, and they could provide rich details from 1 year and 10 years earlier, while controls remembered almost nothing (LePort, Stark, McGaugh, & Stark, 2016). Apparently they're not better learners, but they forget less. Interestingly, total recallers scored as high on an obsession inventory as patients with obsessive-compulsive disorder (OCD). MRI scans revealed enlargement of the caudate nucleus and putamen, both of which are involved in OCD (LePort et al., 2012). Some of them are "germophobes," while others collect things, such as years of old *TV Guides* or hundreds of recorded TV shows; one arranges all the bills in his wallet according to the city of the Federal Reserve Bank where they were issued and how the sports teams in that city did. The researchers suggest this compulsiveness also manifests itself in unintentional rehearsal of past events, which strengthens the memories. Unfortunately, the researchers have not investigated the alternative possibility that total recallers have inadequate active forgetting capabilities.

Reconsolidation

Consolidation is a progressive and dynamic affair, and a consolidated memory is far from "fixed" or permanent (Alberini & LeDoux, 2013). Memories, especially young ones, are vulnerable to disruption from several sources, including electroconvulsive shock and drugs that interfere with protein synthesis. In recent years, researchers have come to realize that each time a memory is retrieved, it must be *reconsolidated*, and during that time, the memory becomes even more vulnerable (Dudai, 2004). For example, Nader, Schafe, and LeDoux (2000) conditioned a fear response (freezing) to a tone in mice by pairing the tone with electric shock to the feet. The antibiotic anisomycin blocks protein synthesis; it will eliminate the fear memory if it is injected shortly after learning, but injection 24 hours after training has no effect. However, as many as 2 weeks later, anisomycin did eliminate the fear response if the researchers induced retrieval of the memory by presenting the tone again (without the shock). You might very well wonder why the brain would give up protection of a consolidated memory during retrieval. Apparently it is because it helps in responding to a changing environment by weakening a now irrelevant memory or strengthening an adaptive one (Alberini & LeDoux, 2013). Rats given several brief exposures to the training apparatus without shock during the first few days after they learned a shock avoidance task showed no forgetting when tested 55 days later (Inda, Muravieva, & Alberini, 2011). Reconsolidation may even have therapeutic usefulness. It can be used to eliminate a learned fear response in humans, and (as you will see in Chapter 14) it could provide an effective tool for erasing fear memories in people with posttraumatic stress disorder (D. Schiller et al., 2010).

Of course, there is no way to guarantee that reconsolidation will always be adaptive; the opportunity to correct errors also allows the introduction of new errors. We have long known that memories get "reconstructed" over time, usually by blending with other memories. Reconstruction can be a progressive affair. Evidence suggests that one reason for the "recovery" of *false* childhood memories during therapy may be therapists' repeated attempts to stimulate recall at successive sessions. Laboratory research has shown that people's agreement with memories planted by the experimenter can increase over multiple interviews (E. F. Loftus, 1997). In one study, researchers using doctored photographs found that after being questioned three times, 50% of subjects were describing a childhood ride in a hot air balloon that never happened (Wade, Garry, Read, & Lindsay, 2002). More recently, Loftus and her colleagues (D. M. Bernstein, Laney, Morris, & Loftus, 2005) were able to shift their subjects' food preferences by giving them a bogus computer analysis of their responses to a food questionnaire. For example, in a follow-up questionnaire, about 20% of the subjects agreed with the analysis that they had, in fact, been made sick by eating strawberry ice cream as children and reported that they would avoid it in the future.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- Make a list of the changes that occur in neurons during learning.
- Describe LTP, LTD, and associative LTP.
- Consolidated memory is both stable and vulnerable. Explain.

LEARNING DEFICIENCIES AND DISORDERS

Learning may be the most complex of human functions. Not surprisingly, it is also one of the most frequently impaired. Learning can be compromised by accidents and violence that damage the structures we have been studying. But more subtle threats to learning ability come from aging and from disorders of the brain, including Alzheimer's disease and other dementias, which we will discuss in this section.

Effects of Aging on Memory

Old Man: Ah, memory. It's the second thing to go.

Young Man: So what's first?

Old Man: I forget …

? Does the brain age, too?

You may or may not find humor in this old joke, but declining memory is hardly a laughing matter to the elderly. The older person might mislay car keys, forget appointments, or leave a pot on the stove for hours. Working memory and the ability to retrieve old memories and to make new memories may all be affected (Fahle & Daum, 1997; Small, Stern, Tang, & Mayeux, 1999). Although we usually associate aging with brain cell loss, significant deficits occur only in the midbrain, basal forebrain (lower frontal lobes), and some prefrontal areas. Some parts of the prefrontal cortex and hippocampus also decline in volume, likely due to a decrease in synaptic density. These areas, of course, are critical for learning, memory, and cognitive functioning (Mora, 2013).

Deficits occur at the molecular level as well. One study, for example, examined the brains of deceased individuals and found 17 genes in the dentate gyrus of the hippocampus that undergo changed levels of expression with aging (Pavlopoulos et al., 2013). Downregulation of one of these genes results in less abundant production of the protein RbAp48 in humans and mice. This protein turns out to be important for memory: Young mice engineered to produce reduced RbAp48 showed dysfunction in the dentate gyrus and performed like old mice on memory tests. In another study, aged mice were significantly impaired on a learning task after just 1 day without practice, but in old mice given a gene that inhibits active forgetting, performance was still robust 4 weeks later (Genoux et al., 2002). If we could find simple, safe ways to manipulate gene expression in humans, we could reduce many of the burdens of aging.

Some elderly people seem immune to the effects of aging on learning and cognition. Certainly, a part of this is genetic, but there have been many research efforts to identify environmental interventions that could benefit the rest of the population. Housing animals in an enriched environment reduces age-related changes in dendritic branching, neurogenesis, spine density, and cortical thickness; physical exercise and calorie restriction have similar effects in animals' brains and improve cognitive functioning in humans (Mora, 2013). We are beginning to appreciate the

value of diet as well. For example, consumption of flavonoids (nutrients found in cocoa, tea, grapes, and apples) enhances functioning in the hippocampal association and is associated with better language and episodic memory and slower cognitive decline in the elderly (Brickman et al., 2014; Vauzour, 2014). In animals, flavonoids have been found to activate cellular learning mechanisms, enhance LTP, and increase hippocampal neurogenesis. There have been additional attempts to improve memory and general cognitive performance in the elderly through computerized training, and meta-analyses indicate moderate improvement in those with mild cognitive impairment and limited gains with dementia (N. T. Hill et al., 2017; H. Zhang et al., 2019).

Alzheimer's Disease

Substantial loss of memory and other cognitive abilities (usually, but not necessarily, in the elderly) is referred to as **dementia**. The most common cause of dementia is **Alzheimer's disease**, a disorder characterized by progressive brain deterioration and impaired memory and other cognitive abilities. Alzheimer's disease was first described by the neuroanatomist and neurologist Alois Alzheimer in 1906, after autopsying the brain of a 56-year-old patient with memory problems. Alzheimer's is primarily a disorder of the aged, although it can strike early in life. Of the nearly 5 million people in the United States with Alzheimer's, 4.7 million are over the age of 65 (Hebert, Weuve, Scherr, & Evans, 2013). The earliest and most severe symptom is usually impaired declarative memory. Initially, the person is indistinguishable from a normally aging individual, though the symptoms may start earlier; the person has trouble remembering events from the day before, mislays items, forgets names, and must search for the right word in a conversation. Later, the person repeats questions and tells the same story again during a conversation. As time and the disease progress, the person eventually fails to recognize acquaintances and even family members. Alzheimer's disease is not just a learning disorder but a disorder of the brain, so ultimately most behaviors suffer. Language, visual-spatial functioning, and reasoning are particularly affected, and there are often behavioral problems, such as aggressiveness and wandering away from home. Alzheimer's researcher Zaven Khachaturian (1997) eloquently described his mother's decline: "The disease quietly loots the brain, nerve cell by nerve cell, like a burglar returning to the same house each night" (p. 21). Eventually, Alzheimer's is fatal, and it is the sixth leading cause of death in the United States (Heron, 2019). If all the dementias were counted together, they would rank as the third leading cause of death, behind heart disease and cancer (Kramarow & Tejada-Vera, 2019). Even those numbers could be low, because doctors often report the immediate cause of death, such as heart or kidney failure, instead of dementia (B. D. James et al., 2014).

The Diseased Brain: Plaques and Tangles

There are two notable characteristics of the Alzheimer's brain, though they are not unique to the disease. **Plaques** are clumps of amyloid beta (Aβ), a type of protein, that cluster among axon terminals and interfere with neural transmission (Figure 12.16a). The main component is Aβ42, so called because it is 42 amino acids long; Aβ42 is particularly "sticky," so it clumps easily to form the plaques. Even in asymptomatic elderly individuals, the presence of plaques is associated with self-reported changes in cognitive function and reduced test performance (Sperling et al., 2020). Aβ42—or, more specifically, the ratio of Aβ42 to Aβ40—leads to the accumulation of the protein tau to form **neurofibrillary tangles** inside neurons; tangles are associated with the death of brain cells (Figure 12.16b; Choi et al., 2014; Kwak et al., 2020). Development of plaques and tangles progresses through the brain in a predictable succession of stages, beginning with the medial cortex and progressing to the limbic areas, particularly the hippocampus, and then to the neocortex, the outer layers of cortex responsible for our highest functions (H. Braak & Braak, 1991). This accounts for the pattern of changing symptoms as the disease advances. We've also learned that this sequence parallels a progressive variation in two significant factors in those areas: the relative level of expression of inflammatory genes and the balance between proteins that promote or inhibit the aggregation

(accumulation and clumping) of plaques and tangles (Figure 12.17; Freer et al., 2016). Studying how the disease develops can be difficult; we don't get a chance to look at the afflicted human brain until the disease is well advanced, and as A Further Look explains, the laboratory models have been less than satisfactory.

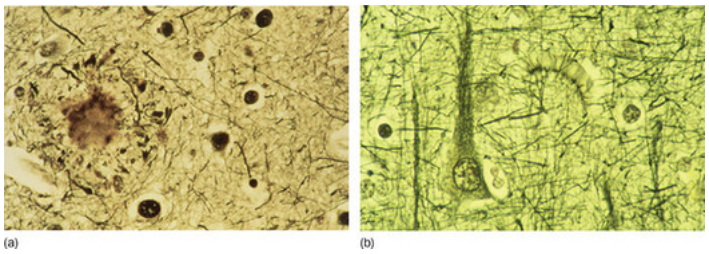
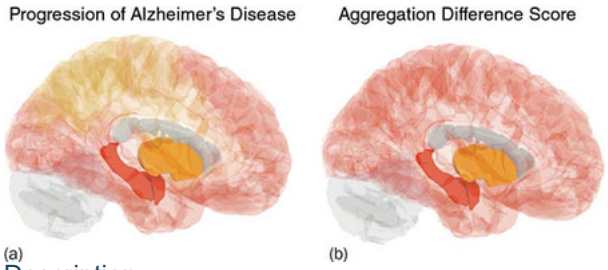


Figure 12.16 Neural Abnormalities in the Brain of a Person With Alzheimer's. (a) The round clumps in the photo are plaques, which interfere with neural transmission. (b) The dark, twisted features are neurofibrillary tangles, which are associated with death of neurons.

Sources: (a) and (b) SPL/Science Source. (b) © SPL/Science Source.



Description

Figure 12.17 Alzheimer's Disease Progress Parallels Aggregation Difference Scores. In (a), the darker the colors, the earlier plaques and tangles appear in that area; gray areas are unaffected. In (b), the darker the colors, the more aggregation promoters exceed aggregation-inhibiting proteins. Note the similarity in the images.

Source: Excerpted from Figure 3 from "A Protein Homeostasis Signature in Healthy Brains Recapitulates Tissue Vulnerability to Alzheimer's Disease," by R. Freer, P. Sormanni, G. Vecchi, P. Ciryam, C. M. Dobson, & M. Vendruscolo, *Science Advances, 2* (8), e1600947.

A Further Look:

Alzheimer's in a Dish

Studying Alzheimer's disease in the laboratory has been difficult because the models used so far don't duplicate the pathology completely. Mice can be genetically engineered to produce the amyloid plaques but not the neurofibrillary tangles, and cultures of neurons from Alzheimer's patients' brains produce amyloid and tau but not the plaques and tangles. Researchers at Massachusetts General Hospital realized that the two-dimensional liquid cultures used in the laboratory are very different from the gelatinous environment of the brain, so they started using a three-dimensional gel to grow their cultures; to this they added stem cells that carried two gene variants known to cause Alzheimer's (Choi et al., 2014). After 6 weeks, the culture had both the typical amyloid and the toxic form of amyloid and was complete with plaques and tangles. When the researchers blocked the formation of plaques, they obtained the first direct evidence that plaque formation is a precursor to the development of the synapse-damaging tangles. More recently, 3-D gel technology helped scientists determine that the Aβ42/Aβ40 ratio, rather than total Aβ42, determines tangle formation (Kwak et al., 2020).

What causes Alzheimer's disease?

Our understanding of these mechanisms continues to evolve. Researchers now distinguish between insoluble and soluble forms of amyloid. The soluble form has been linked to synapse loss, memory failure, and failure of LTP in the hippocampus of mice (Gong et al., 2003), and it is 70 times more plentiful in the brains of people with Alzheimer's (M. E. Larson & Lesné, 2012). More recently, we have learned that a modified form of tau, called *acetylated* tau (because of an added acetyl group), is particularly important because it depletes a protein (KIBRA) that is required for inserting extra receptors into the neuronal membrane during learning (Tracy et al., 2016). Increasing KIBRA levels in cultured neurons reversed the effects of acetylated tau and restored their ability to strengthen connections, suggesting a new therapeutic approach.

Figure 12.18 compares the brain of a deceased Alzheimer's patient with a normal brain. Notice the decreased size of the gyri and the increased width of the sulci in the diseased brain. Internally, enlarged ventricles tell a similar story of severe neuron loss. Many of the lesions are in the temporal lobes; because of their location, they effectively isolate the hippocampus from its inputs and outputs, which partly explains the early memory loss (B. T. Hyman, Van Horsen, Damasio, & Barnes, 1984). However, plaques and tangles also attack the frontal lobes, accounting for additional memory problems as well as attention and motor difficulties. The occipital lobes and parietal lobes also may be involved; disrupted communication between the primary visual area and the visual association areas in the parietal and temporal lobes explains the visual deficits that plague some Alzheimer's sufferers.

Figure 12.18 Normal Brain (Left) and Alzheimer's Brain.
The illustration shows the most obvious differences, the reduced size of gyri and the increased size of sulci produced by cell loss in the diseased brain.

Source: REUTERS/Denis Balibouse.

Heredity and Environment

The first clue to a gene location came from a comparison of Alzheimer's with Down syndrome (Lott, 1982). Down syndrome individuals also have plaques and tangles, and they invariably develop Alzheimer's disease if they live to the age of 50. Because Down syndrome is caused by an extra chromosome 21, researchers zeroed in on that chromosome; there they found mutations in the *amyloid precursor protein (APP)* gene (Goate et al., 1991). When aged mice were genetically engineered with an *APP*

mutation that increased plaques, both LTP and spatial learning were impaired (Chapman et al., 1999). Three additional genes that influence Alzheimer's had been confirmed by the end of the 1990s; all those genes affect amyloid production or its deposit in the brain (Selkoe, 1997). As you can see in Table 12.1, the genes fall into two classes, one associated with early-onset Alzheimer's disease (often before the age of 60) and one found in patients with late-onset Alzheimer's. The ε4 allele of the *APOE* gene is particularly interesting because it contributes to so many Alzheimer's cases. It increases risk by three- to eight-fold and is associated with plaques and tangles, but how it contributes to pathology is not well understood. Two studies indicate that carriers without dementia have lower cerebral blood flow (Thambisetty, Beason-Held, An, Kraut, & Resnick, 2010) and that 2- to 25-month-old children with the allele have reduced growth in temporal and parietal areas, which are affected in patients with Alzheimer's (Dean et al., 2014).

Table 12.1

TABLE 12.1 Known Genes for Alzheimer's Disease.

GENE	CHROMOSOME	AGE OF ONSET (YEARS)	PERCENTAGE OF CASES
APP	21	45–66	< 0.1
Presenilin 1	14	28–62	1–2
Presenilin 2	1	40–85	< 0.1
ApoE4	19	> 60	> 50

Sources: Marx (1998); Selkoe (1997).

Sources: Marx (1998); Selkoe (1997).

The four genes in the table account for just a little more than half the cases of Alzheimer's disease, so there are likely many rare or small-effect genes as well as environmental influences. Discovery of additional genes had to await whole-genome studies with large numbers of individuals. Such studies have the advantage that they allow gene searches without the need for a preconceived target area. Prior to 2009, 11 genes had been associated with Alzheimer's, but a whole-genome study of 74,000 individuals was able to add 11 additional gene locations (Lambert et al., 2013). Although the genes themselves have not been identified yet, genes near the loci are involved in amyloid and tau pathways, inflammation, immune response, cell migration, and cellular functions.

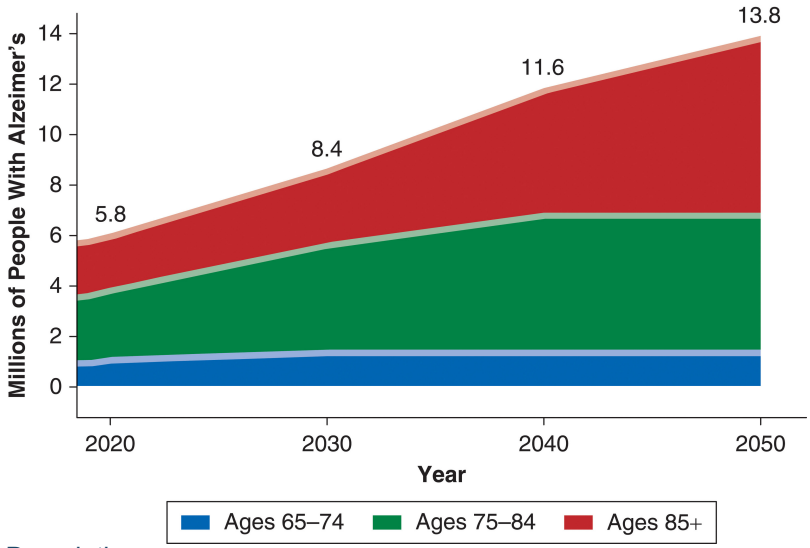
Genome-wide studies have also made it possible to do broad searches for epigenetic changes, and in the past few years, the focus has been shifting in that direction. A recent study conclusively identified seven genes that were differently methylated in Alzheimer's patients by taking the unusual step of verifying their results in a second group of subjects (P. L. De Jager et al., 2014). Identifying the environmental conditions that trigger these changes could help us reduce the incidence of Alzheimer's. A meta-analysis indicated several environmental risks for dementia, including exposure to pesticides, fertilizers, herbicides, and insecticides; airborne particulate matter; secondhand smoke; and electromagnetic fields (Killin, Starr, Shiue, & Russ, 2016). We've also learned that neurons can modify their RNA through a process called *somatic recombination*. We've known for years that immune cells use this strategy to adapt to new threats. Ming-Hsiang Lee and colleagues (2018) discovered that neurons from the brains of Alzheimer's patients had six times as many varieties of the *APP* gene as in healthy people, including 11 mutations already known to be linked to the inherited form of Alzheimer's.

On the general health side, we can add vitamin D deficiency (Killin et al., 2016), diabetes, obesity, smoking, and hypertension as risk factors (Baumgart et al., 2015). A study of more than 1 million women found that mid-life obesity was associated with a 21% increase in Alzheimer's risk 20 years later (Floud et al., 2020). Researchers are also beginning to recognize a likely role for infection and inflammation. When gum infection was induced in mice, the *P. gingivalis* bacteria invaded the hippocampus, resulting in amyloid plaques and neural damage (Llievski et al., 2018). There is also evidence from mouse studies that infection and inflammation can induce microglia, which normally remove amyloid, to begin removing synapses. Other

environmental influences also appear to trigger this response, such as sleep deprivation (Rajendran & Paolicelli, 2018). In humans, a meta-analysis found a five-fold increase in risk for Alzheimer's with *Chlamydophila pneumoniae* bacterial infection and a 10-fold increase with spirochete infection (Maheshwari & Eslick, 2015). Indeed, there is increasing evidence that amyloid increases during infection and acts as an antimicrobial agent. In the laboratory, amyloid protected human neural cells from *Candida* infection and roundworms from infection by *Candida* and *Salmonella*, and it significantly extended the survival time of mice after *Salmonella* infection (Kumar et al., 2016).

Treatment of Alzheimer's Disease

The past few years have seen a substantial drop in the number of cases of dementia in high-income countries, including a 26% decrease in the United States (Langa, 2015; Langa et al., 2017). The reasons are believed to be increasing education and more aggressive treatment of cardiovascular diseases. The outlook for Alzheimer's disease is very different, however, driven largely by an aging population. About 97% of Alzheimer's patients—5.8 million people—are age 65 or older; this age group is expected to increase 60% by the year 2050. Unless a cure is found, the number of people over 65 with Alzheimer's disease is projected to more than double, reaching 13.8 million (Figure 12.19; Alzheimer's Association, 2020).



Description

Figure 12.19 Projected Increase in the Number of People Age 65 and Older With Alzheimer's Disease.
Notice the sharp increases not only in the number of cases but in the number of older people, especially in the 85+ group.

Sources: Based on data from Hebert et al. (2013) and Alzheimer's Association (2020).

Researchers are desperately seeking a cure for Alzheimer's. Unfortunately, the five drugs that are currently approved for the treatment of Alzheimer's in the United States offer benefits so small that they often don't justify the side effects (Table 12.2). Three of the drugs are cholinesterase inhibitors; they restore acetylcholine transmission by interfering with the enzyme that breaks down acetylcholine at the synapse. Acetylcholine is important for attention, memory, and motivation, and acetylcholine-releasing neurons are significant victims of degeneration in Alzheimer's disease. The fourth drug, memantine (marketed in the United States as Namenda), was the first approved for use in patients with moderate and severe symptoms. Some of the neuron loss in Alzheimer's occurs when dying neurons trigger the release of the excitatory transmitter glutamate; the excess glutamate produces excitotoxicity,

overstimulating NMDA receptors and killing neurons. Memantine limits the neuron's sensitivity to glutamate, reducing further cell death. Studies indicate moderate slowing of deterioration and improvement in symptoms (Reisberg et al., 2003; U.S. Food and Drug Administration, 2003). Unfortunately, these drugs treat only the symptoms, not the underlying cause, and they are little or no help when degeneration is advanced.

Table 12.2

TABLE 12.2 Drugs Approved for Treating Alzheimer's Disease in the United States

BRAND/GENERIC	APPROVED FOR	BENEFITS	SIDE EFFECTS
Aricept/donepezil	All stages	Inhibits cholinesterase; small improvement on memory and thinking tests; slowed progress of symptoms	Nausea, vomiting, appetite loss, increased frequency of bowel movements
Razadyne/galantamine	Mild to moderate		
Excelon/rivastigmine	Mild to moderate		
Namenda/memantine	Moderate to severe	Regulates glutamate; small improvement in mental function and daily activities	Headache, constipation, confusion, dizziness
Namzaric/memantine plus donepezil	Moderate to severe	Improvement in cognition and mental function; slowed progress of symptoms	Nausea, vomiting, appetite loss, increased frequency of bowel movements, headache, constipation, confusion, dizziness

Source: Alzheimer's Association (n.d.-a)

Source: Alzheimer's Association (n.d.-a)

Much of current research is focused on removing Aβ or blocking its formation and preventing tau from forming tangles. After a string of failures with other anti-amyloid drugs, most of the patients treated with aducanumab were declared amyloid free; unfortunately, there was only minimal evidence of symptom improvement (Sevigny et al., 2016). A later Phase 3 trial was halted for lack of results, but the researchers then analyzed the data of patients who had chosen to continue taking the drug and found the results were positive enough that the manufacturer is asking the FDA to make aducanumab the first Alzheimer's drug to receive approval since 2003 (P. Anderson, 2019). Two other research teams also received surprises after their Phase 3 trials had failed to show improvements. They had made the unusual choice of giving patients in their control groups tiny "placebo" doses of their tau inhibitors (hydromethylthionine in one case and LMTM in the other). In both studies, patients receiving the 25-times stronger therapeutic doses were unimproved at the end of the trials, but the controls had dramatic reductions in brain atrophy and significant improvement in cognitive functioning (Schelter et al., 2019; Wilcock et al., 2018). Further studies, of course, are underway to confirm the results and determine the most effective dosages.

A novel treatment was suggested by a study with mice engineered to produce abundant plaques. Stimulating their brains with pulses of ultrasound activated glial cells and reduced plaque levels, presumably because the glia ingested them. As a result, the mice regained their lost memory capability (Leinenga & Götz, 2015). When patients were treated with ultrasound, memory-related areas in their brains became more active and their test performance improved for up to 3 months (Beisteiner et al., 2020).

Whether pathology progresses from amyloid plaques to tangles depends on inflammation. The accumulation of Aβ triggers an immune response in microglia, which release the inflammatory agent NLRP3 inflammasome (Ising et al., 2019). This results in chemical changes in tau that cause it to become sticky and form into clumps. We've known about the association between neural inflammation and Alzheimer's for years, but now NLRP3 provides a potentially important new target for reducing tau.

Stem cell therapy is an obvious treatment possibility, which holds promise on a number of fronts. Stem cells not only can induce regeneration of neurons and synapses; they also combat microglia-initiated inflammation (S.-M. Wang, Lee, & Lim, 2019). The work is in its early stages, but two clinical trials have been completed, and nine others are underway. On the gene therapy front, researchers plan to take advantage of the fact that the *ApoE2* allele is protective against Alzheimer's. Inserting *ApoE2* genes into mice engineered to show Alzheimer's pathology markedly reduced their amyloid levels (L. Zhao et al., 2016). A clinical trial is now recruiting volunteers to

test the procedure on patients homozygous for *ApoE4* (“Gene Therapy for APOE4 Homozygote of Alzheimer’s Disease,” 2019).

Detecting Alzheimer’s Disease

The aging individual dealing with memory problems typically wonders, “Am I getting Alzheimer’s?” No single test can diagnose Alzheimer’s. Most often, the individual will take a battery of memory and cognitive tests; the pattern of deficits will help identify the cause as Alzheimer’s while ruling out other dementias. The physician may also order an MRI to look for atrophy in the temporal and parietal areas or a PET scan to identify areas of reduced activity. Using new tracers that target Aβ and tau, PET scans can identify 75% to 90% of individuals who are later confirmed by autopsy to have Alzheimer’s (Fraller, 2013).

Biological assessment should lead to more appropriate treatment planning by differentiating better between Alzheimer’s and other dementias; in addition, it will be possible to monitor therapeutic progress, detecting changes before they have time to translate into cognitive gains. But because current treatments only slow the progress of Alzheimer’s, researchers are interested in detecting the disease well before it is full-blown and before irreversible damage has occurred. PET scanning for amyloid predicts about one third of individuals with mild cognitive impairment who will be diagnosed with Alzheimer’s during the next several months; among the normal elderly, 25% with high amyloid levels are diagnosed within 3 years, while those with low levels have a 98% chance of remaining cognitively stable (Gelosa & Brooks, 2012). Detection of Aβ and tau in cerebrospinal fluid has shown 98% to 100% accuracy in identifying individuals who developed Alzheimer’s within the next 5 to 6 years (De Meyer et al., 2010; Khan & Alkon, 2010). Although this test differentiates Alzheimer’s from fronto-temporal dementia, it does not distinguish some others, such as Lewy body dementia (Paterson et al., 2018).

A study of Roman Catholic sisters that has been going on since 1986 revealed cognitive differences as many as five decades before some of them were diagnosed with Alzheimer’s (Riley, Snowdon, Desrosiers, & Markesbery, 2005). Autobiographical essays were available for 180 of the study participants, written when they joined the order at an average age of 22. These were scored for idea density, defined as the number of ideas expressed for every 10 words. Almost 80% of the sisters with the lowest density scores eventually developed Alzheimer’s, compared with 10% among those who scored the highest. A surprising finding was the number of participants with high density scores and no symptoms of Alzheimer’s who had neurofibrillary tangles when they were autopsied (D. Iacono et al., 2009; Riley et al., 2005). Also, the sisters who remained healthy were just as likely as the ones with Alzheimer’s to have one or more *ApoE4* alleles (Riley et al., 2005). So what protected some of the women from Alzheimer’s? This question leads us to the reserve hypothesis.

Resistance to Alzheimer’s: The Reserve Hypothesis

According to the **reserve hypothesis**, individuals with greater cognitive or brain capacity can compensate for brain changes due to aging, brain damage, or disorders such as Alzheimer’s. There is some evidence for compensation in the elderly through *brain reserve*, either by means of greater activation in the network involved or by recruiting other brain areas (reviewed in Stern, 2012). However, most studies have focused on *cognitive reserve*, by assessing experiential factors and cognitive capabilities. For example, the risk of developing the symptoms of dementia decreases by 46% with higher educational and occupational levels and higher IQ and mental activity in earlier life. This compensation is an effortful activity; fMRI showed that older people with more amyloid deposits produced more activation in their brains’ memory areas, and they were more accurate in recalling material when they did so (Elman et al., 2014). The protection this affords is temporary, however; the delay may last the rest of the individual’s life, but if not, decline occurs more rapidly than in other Alzheimer’s patients.

The elderly fare better if they have a history of both mental and physical activity, so they are frequently advised to stay active to stave off mental decline. However, choosing an active lifestyle may simply be a reflection of general fitness, rather than the cause of better cognitive health later; we should be careful about assuming cause until we have adequate experimental evidence, and so far, the results have been mixed. The most consistently positive results have been with exercise, and we mentioned some promise from cognitive training.

Other Dementias

Alzheimer's accounts for 60% to 80% of all cases of dementia. Second is vascular dementia, also called vascular cognitive impairment, at 5% to 10%. It is caused by loss of blood supply to a part of the brain, for example, by stroke; in memory-related areas, this produces Alzheimer's-like symptoms, and in other areas, the result can include confusion, motor problems, and language impairment. The third most common type of dementia is fronto-temporal dementia. It is most often caused by the accumulation of tau, or of the protein TDP-43. It differs from Alzheimer's in its greater language impairment and later onset of memory problems (Alzheimer's Association, n.d.-b).

A less common (though likely underdiagnosed) form of dementia is Korsakoff syndrome, brain deterioration that is almost always caused by chronic alcoholism. The damage is due to a deficiency in thiamine (vitamin B1), which is needed to produce energy from sugar. Alcohol reduces thiamine absorption in the stomach, and the situation is made worse because the alcoholic tends to forgo food in favor of alcohol. Korsakoff syndrome impairs declarative memory, especially anterograde, without affecting nondeclarative forms. Thiamine therapy can relieve the symptoms of Korsakoff syndrome somewhat if the disorder is not too advanced, but the brain damage itself is irreversible. The hippocampus and temporal lobes are unaffected in Korsakoff syndrome, but the mammillary bodies (see Figure 8.4) and the medial thalamus are reduced in size, and structural and functional abnormalities occur in the frontal lobes (Gebhardt, Naeser, & Butters, 1984; Kopelman, 1995; Squire, Amaral, & Press, 1990). A bizarre accident demonstrated that damage limited to the thalamic and mammillary areas can cause anterograde amnesia; a 22-year-old college student received a penetrating wound to the area when his roommate accidentally thrust a toy fencing foil up his left nostril, producing an amnesia that primarily affected verbal memory (Squire, Amaral, Zola-Morgan, Kritchevsky, & Press, 1989).

? What are the symptoms of Korsakoff syndrome?

Some Korsakoff patients show a particularly interesting characteristic in their behavior, called **spontaneous confabulation**; they fabricate stories and facts to make up for those missing from their memories. Patients with other memory disorders also confabulate when they are asked a question and their memory is inadequate, and normal individuals do, too, but provoked confabulation has a different mechanism from the "creative remembering" of spontaneous confabulation. We will talk about what causes confabulation shortly; in the meantime, try to refrain from assuming that confabulation involves intentional deception.

For some, spontaneous confabulation becomes a way of life. Mary Frances could converse fluently about her distant past as a college and high school English teacher and recite Shakespeare and poetry that she had written. But robbed of the memory of more recent years by Korsakoff disease, she constantly invented explanations for her nursing home surroundings. One time, she was just "visiting" at the home, and she watched patiently through the glass front doors for her brother who would pick her up shortly for an automobile trip to Florida. Another time, she complained that she was stranded in a strange place and needed to get back to her "post"; she had, in fact, been in the army in World War II as a speechwriter for General Clark. On another occasion, she thought that she was in prison—probably suggested by the real memory that she had been a prisoner of war—and she was querying the nurse about what she had "done wrong."

Spontaneous confabulation may be brief or long lasting, depending on the extent and location of the damage. A Korsakoff patient studied by Benson and his colleagues (1996) had reduced activity in frontal areas and in the diencephalon, the area that includes the thalamus and hypothalamus. Four months later, he had ceased confabulating, and the scan of the frontal area had returned to normal; however, his general amnesia and deficient diencephalic activity continued. Scanning studies with healthy individuals and patients show that the orbitofrontal cortex suppresses irrelevant memories through its subcortical connections (Schnider, 2003). Most researchers believe that confabulators such as Mary Frances fabricate false memories from older, irrelevant ones, due to an inability to suppress them or to distinguish them from contemporary memories. In support of their position, they point out that spontaneous confabulation ceases at the same time the person recovers the ability to identify the time period of memories (Dalla Barba & La Corte, 2015; Schnider, 2003). We will take up this topic again in Chapter 15.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- What changes occur in the brain during aging?
- What is the role of plaques and tangles in Alzheimer's disease?
- How are Alzheimer's disease and Korsakoff syndrome similar and different?

IN PERSPECTIVE

Learning is a form of neural plasticity. However, that simple statement ignores a variety of complex features that characterize learning. For example, different kinds of learning can be impaired selectively, as we see in patients who can learn and yet have no recollection of having learned. Our exploration of learning has been an abbreviated one, partly because of the complexity of the subject, but also because many mysteries are still waiting to be solved.

Despite all we know about the learning process, we have little ability to enhance it. Researchers tell us that blueberries can reduce learning deficits in aging rats and that wearing a nicotine patch can improve memory, but they can do disappointingly little to help the Alzheimer's patient. Curing learning disorders and improving normal learning ability are little more than aspirations today. But there is good reason to think the mysteries will be solved eventually, perhaps with your help.

Chapter Summary

Learning as the Storage of Memories

- Brain damage can cause amnesia by impairing the storage of new memories (anterograde) or the retrieval of old memories (retrograde).
- The hippocampus is involved in both consolidation and retrieval. The prefrontal area may play an executive role.
- Memories are stored near the area where the information they are based on is processed.
- There are at least two kinds of learning: declarative, mediated by the hippocampus, and nondeclarative, which involves the striatum and amygdala.
- Working memory holds new information and information retrieved from storage while it is being used.

Brain Changes in Learning

- LTP increases synaptic strength, and LTD reduces it.
- LTP is necessary for learning; diminishing it impairs learning, and increasing it enhances learning.
- The hippocampus manages new declarative memories, but they are transferred later to the cortex.
- Changes at the synapse include protein activation and increases in the number of AMPA receptors and the number of dendritic spines. Increased neurogenesis in the hippocampus appears to aid memory transfer to the cortex.

Learning Deficiencies and Disorders

- Aging usually involves some impairment of learning and memory, but in the normally aging brain, substantial loss of neurons and synapses is limited to a few areas.
- Alzheimer’s disease is a hereditary disorder that impairs learning and other brain functions, largely through the destruction of acetylcholine-producing neurons. Treatment usually involves increasing acetylcholine availability, but experimental treatments take other approaches.
- Frontotemporal and Lewy body dementias are second and third to Alzheimer’s in frequency. Korsakoff syndrome, due to thiamine deficiency resulting from alcoholism, impairs declarative memory, especially anterograde. A frequent characteristic of Korsakoff syndrome is spontaneous confabulation.

Study Resources

For Further Thought

- If you were building an electronic learning and memory system for a robot, is there anything you would change from the human design? Why or why not?
- What are the learning and behavioral implications of impaired working memory?
- What implication does the experiment in which mice were injected with the antibiotic anisomycin at the time of retrieval have for your study conditions as you review material for an exam?
- Which direction of research for the treatment of Alzheimer's do you think holds the greatest promise? Why?

Test Your Understanding

1. Discuss consolidation, including what it is, when and where it occurs, and its significance in learning and memory.
2. Make the argument that LTP provides a reasonably good explanation of learning, including some of learning's basic phenomena.
3. Compare Alzheimer's disease and Korsakoff syndrome in terms of causes, symptoms, and brain areas affected.

Select the best answer:

1. Anterograde amnesia means that the patient has trouble remembering events that occurred
    1. more than a few minutes earlier.
    2. before the brain damage.
    3. since the brain damage.
    4. since the brain damage and for a few years before.
2. If you are positive you know who the 14th president of the United States is but cannot remember at this very moment, you are having a problem with
    1. consolidation.
    2. retrieval.
    3. amnesia.
    4. dementia.
3. The main neurotransmitter implicated in memory formation is
    1. serotonin.
    2. epinephrine.
    3. endorphin.
    4. dopamine.
4. If H. M.'s striatum had also been damaged, he would also not have remembered
    1. declarative memories of childhood events.
    2. skills learned before his surgery.
    3. skills learned after his surgery.
    4. emotional experiences after his surgery.
5. In the course of adding a long column of entries in your checkbook, you have to carry a 6 to the next column. If you forget the number in the process, you're having a problem with
    1. consolidation.
    2. LTP.
    3. retrieval.
    4. working memory.
6. The researcher sounds a tone and then delivers a puff of air to your eye. After several times, the tone alone causes you to blink. This behavior is best explained by
    1. LTP.
    2. associative LTP.
    3. LTD.
    4. associative LTD.
7. Synaptic changes during learning involve
    1. activation of proteins.
    2. an increased number of dendritic spines.

3. an increased number of receptors.
4. All of the above

8. When do most of the genes linked to memory consolidation increase their activities?
    1. During sleep
    2. During times of relaxation
    3. During long bouts of studying
    4. When you are distracted
9. Memories are vulnerable to the insertion of “false facts” through suggestions or ideas that fill in the gaps. This usually occurs during the process of
    1. extinction.
    2. consolidation.
    3. retrieval.
    4. reconsolidation.
10. When researchers injected anisomycin, which blocks protein synthesis, into the brains of mice 2 weeks after fear conditioning, the results demonstrated that
    1. protein increase improves memory.
    2. antibiotics can improve memory.
    3. memories are particularly vulnerable during recall.
    4. once recalled, a memory takes longer to reconsolidate.
11. The aged brain is characterized by substantial ____ throughout the cortex.
    1. loss of neurons
    2. loss of synapses
    3. decrease in metabolism
    4. All of the above
    5. None of the above
12. Alzheimer’s disease is most closely associated with
    1. plaques and tangles.
    2. the APP gene.
    3. environmental toxins.
    4. All of the above
13. The feature most common between Alzheimer’s disease and Korsakoff syndrome is the
    1. symptoms.
    2. age of onset.
    3. degree of hereditary involvement.
    4. degree of environmental contribution.

Answers:

1. c, 2. b, 3. d, 4. c, 5. d, 6. b, 7. d, 8. a, 9. d, 10. c, 11. e, 12. a, 13. a.

For Further Reading

1. *The Cognitive Neuroscience of Memory*, by Scott Slotnick (Cambridge University Press, 2017), covers the brain mechanisms underlying long-term memory and its failure, working memory, and diseases of memory.
2. *The Cognitive Neuroscience of Memory Consolidation*, edited by Nikolai Axmacher and Björn Rasch (Springer, 2017), provides an in-depth treatment of that topic.
3. In “Neurogenesis Erases Existing Memories,” by Leonie Welberg (*Nature Reviews Neuroscience*, 2014, *15*, 428–429), the author presents evidence that hippocampal neurogenesis not only promotes the formation of new memories but also induces forgetting of established ones.
4. “Place Cells, Grid Cells, and Memory,” by May-Britt Moser, David C. Rowland, and Edvard Moser (*Cold Spring Harbor Perspectives in Biology*, 2015, *7*, a021808, available at http://cshperspectives.cshlp.org/content/7/2/a021808.full), goes beyond place cells to describe a whole network that provides our maps of space.
5. “Secrets of an Age-Resistant Memory,” by Jessica Hamzelou (*New Scientist*, September 10, 2016), describes a project studying people who qualify as “superagers” by being over the age of 80 but performing like 55-year-olds on memory tests.

Key Terms

Alzheimer's disease 406

anterograde amnesia 391

associative long-term potentiation 400

consolidation 392

declarative memory 397

dementia 406

dendritic spines 402

Hebb rule 399

long-term depression (LTD) 399

long-term potentiation (LTP) 399

neurofibrillary tangles 407

nondeclarative memory 397

place cells 395

plaques 407

reserve hypothesis 413

retrieval 392

retrograde amnesia 391

spontaneous confabulation 414

working memory 398

Descriptions of Images and Figures

Back to Figure

1. Two brain scans show the coronal view of H.M.'s brain and normal brain. H.M.'s brain has smaller ventricles, and the structures labeled M M N, A, H, C S, P R, and E C in the normal brain on the ventral surface of the brain are absent or partially absent in H.M.'s brain.
2. The parts labeled in the medial temporal lobe are hippocampus and parahippocampal gyrus.

Back to Figure

The horizontal axis is labeled Time and the vertical axis is labeled Memory strength. The curve for short-term memory, lasting seconds to hours, rises a sharp peak in a short time, decreases, and touches the horizontal axis after a moderate amount of time. The curve for long-term memory, lasting hours to months, rises gradually to a lower peak, decreases, and touches the horizontal axis after a longer time. The curve for long-lasting memory, lasting months to lifetime, rises slowly.

Back to Figure

1. Low recall minus baseline: The scan is labeled positive 6 millimeters. Z cubed 3.00, p less than 0.001. The regions activated in yellow are some regions in the prefrontal cortex and occipital lobe.
2. High recall minus baseline: The scan is labeled negative 2 millimeters. Z cubed 3.00, p less than 0.001. The regions activated in red are the hippocampus.

Back to Figure

The regions highlighted are as follows.

- Perception of pictures: Most regions of the occipital lobe.
- Recall of pictures: Arrows point to the smaller regions of activation in the occipital lobe. The same regions were activated during perception.
- Perception of sounds: Most regions in the posterior lateral side of the brain.
- Recall of sound: Arrows point to the few regions activated in the left lateral side of the brain. These regions were also activated during perception.

Back to Figure

1. Stimulation by weak synapse (test): When a neuron is stimulated through a weak synapse, the activation is low.
2. Stimulation by weak and strong synapse (induction): When a neuron is stimulated through strong and weak synapses, the activation is high.
3. Stimulation by strengthened synapse (test): When a neuron is stimulated through a strengthened synapse, the activation is high.

Back to Figure

1. A dendrite consists of A M P A receptor and N M D A receptor. Axon releases glutamate molecules, which attach themselves to the receptors. Positive sodium ion enters the cell through A M P A receptor, and magnesium ion blocks N M D A receptor.
2. The much depolarized dendrite consists of A M P A receptor and N M D A receptor. Axon releases glutamate molecules repeatedly, which attach themselves to the receptors. More positive sodium ion enters the cell through A M P A receptor. Magnesium ion is displaced from N M D A receptor, and positive sodium and calcium ions enter the cell.

Back to Figure

The horizontal axis is labeled Retention delays (days) and ranges from 1 to 50. The vertical axis is labeled Percentage animals freezing, and ranges from 0 to 100 in increments of 25. The approximate data from the graph are tabulated below.

Back to Figure

1. Progression of Alzheimer’s disease: The shading of different regions of the brain in the increasing order of darkness are as follows: Cerebellum, cingulate gyrus, parietal lobe, frontal lobe and temporal lobe, thalamus, and parahippocampal gyrus.
2. Aggregation difference score: Cerebellum and cingulate gyrus are shaded light, frontal, parietal, temporal, and occipital lobes are shaded dark, and thalamus and parahippocampal gyrus are shaded the darkest.

Back to Figure

The horizontal axis is labeled year, and ranges from 2020 to 2050 in increments of 10. The vertical axis is labeled millions of people with Alzheimer’s, and ranges from 0 to 14, in increments of 2. The approximate data from the graph are tabulated below.

13 INTELLIGENCE AND COGNITIVE FUNCTIONING

Monkey Business Images / Shutterstock

The Nature of Intelligence

What Does “Intelligence” Mean?

The Structure of Intelligence

Concept Check

The Biological Origins of Intelligence

The Brain and Intelligence

Specific Abilities and General Intelligence

A Further Look | We Aren’t the Only Tool Users

Heredity and Environment

Concept Check

Deficiencies and Disorders of Intelligence

Effects of Aging on Intelligence

A Further Look | Enhancing Intelligence and Cognitive Performance

Intellectual Disability

Autism Spectrum Disorder

A Further Look | Childhood Vaccines and Autism

Attention-Deficit/Hyperactivity Disorder

Concept Check

In Perspective

Chapter Summary

Study Resources

After reading this chapter, you will be able to

13.1 Describe how scientists have defined intelligence.

13.2 Critique the methods for measuring intelligence.

13.3 Identify how the structure of the nervous system relates to intelligence.

13.4 Appraise the relative contributions of heredity and environment to intelligence.

13.5 Assess the impact of the typical aging process on cognitive functioning.

13.6 Compare the impacts of intellectual disability, autism, and attention-deficit/hyperactivity disorder on intelligence.

Some people believe that the late Cambridge theoretical physicist Stephen Hawking was the most brilliant person of our time. Following in Einstein's footsteps, he developed theories of the origin of the universe that altered the way scientists think. He lectured around the world, mixing high-powered physics with a keen sense of humor. He achieved all this despite having Lou Gehrig's disease (*amyotrophic lateral sclerosis*, or *ALS*), a degenerative disease that impairs voluntary movement. Confined to a wheelchair and able to make only small facial movements, he wrote and spoke by moving a cursor on the screen of a computer equipped with a voice synthesizer (Figure 13.1).

Figure 13.1 Stephen Hawking.
His great intellect resided in a body that could communicate only by moving a cursor on a computer screen.

Source: Jemal Countess/Singer/Getty Images Entertainment/Getty Images.

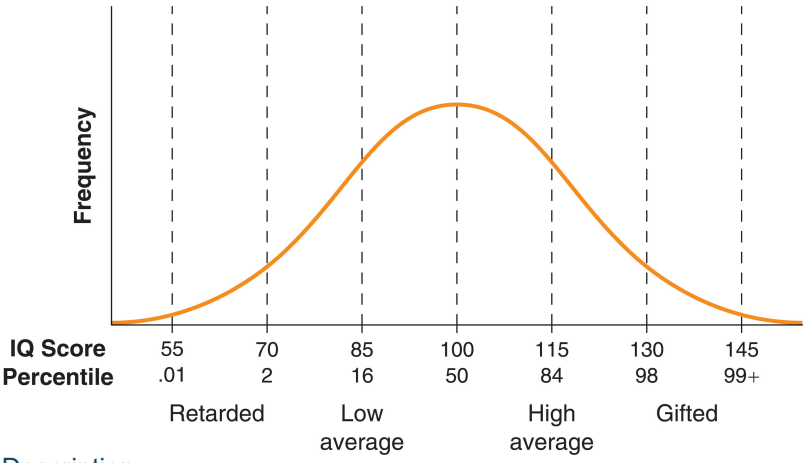
When we consider people like Hawking, we are forced to wonder what makes one person more intelligent than another. Is it genes, upbringing, hard work, or opportunity? And is the ultra-intelligent brain in some way different? Unfortunately, we have a problem with the presumption of *who* is smarter. Was Hawking more intelligent than Einstein, or did he just have the advantage of more predecessors' accomplishments to build on? Was Marilyn vos Savant smarter than her husband because at the age of 10 she made the highest score ever recorded on an intelligence test (Yam, 1998), while he had trouble testing well enough to get into medical school, or is he smarter because he invented the Jarvik artificial heart? We cannot attempt to understand the biological bases of intelligence without having some appreciation of our limitations in measuring it or even defining what it is.

THE NATURE OF INTELLIGENCE

There are many ideas about what intelligence is, which is the first clue that we don't have consensus about what it is. Most definitions say something to the effect that **intelligence** is the ability to reason, to understand, and to profit from experience. That is what we *think* intelligence is; the problem comes when we try to translate that abstract definition into the behaviors that would indicate the presence of intelligence. That is what we must do to measure intelligence, which is the first step toward determining its biological basis.

What Does "Intelligence" Mean?

Understanding how we measure intelligence is important because we are in effect defining intelligence as *what that test measures*. The measure of intelligence is typically expressed as the **intelligence quotient (IQ)**. The term originated with the scoring on early intelligence tests designed for use with children. The tests produced a score in the form of a *mental age*, which was divided by the child's chronological age and multiplied by 100. The tests were designed to produce a score of 100 for a child performing at the average for his or her chronological age. The scoring is completely different now, partly because the tests were extended to adults, who do not increase consistently in intellectual performance from year to year. The base score is still 100, a value selected arbitrarily and preserved artificially by occasional adjustments to compensate for any drift in performance in the population. Most people are near the average, as Figure 13.2 shows, with relatively few people at either of the extremes. For example, only 2% of the population score above 130 points or below 70 points.



Description

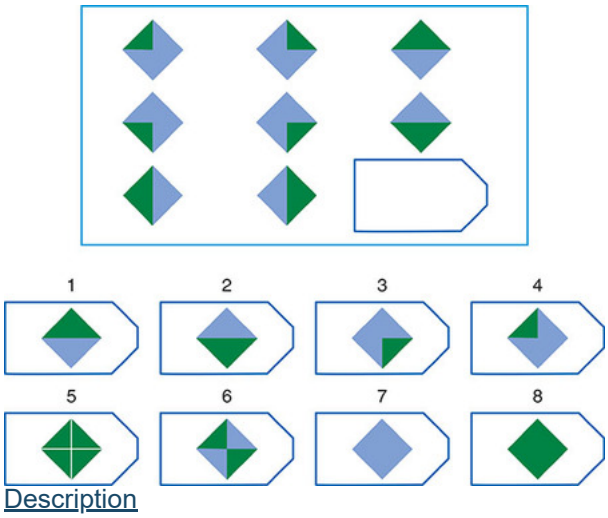
Figure 13.2 Distribution of IQ Scores in the Population.

Source: From *Psychology: The Adaptive Mind* (2nd ed.), by J. S. Nairne, 2000, Wadsworth, a part of Cengage Learning, Inc. Reproduced by permission from the Author.

The first intelligence test was devised by Alfred Binet in 1905, to identify French schoolchildren who needed special instruction (Binet & Simon, 1905). Predicting school performance is still what most intelligence tests do best, and intelligence tests have found their greatest use in the school setting. The correlation between IQ scores and school grades typically falls in the range of .40 to .60 (Kline, 1991). (If you've forgotten what a correlation coefficient means, see page 112 in Chapter 4.) However, IQ is also related to job performance, income, and socioeconomic level and, negatively, to juvenile delinquency (Neisser et al., 1996). Intelligence is also stable: Results of tests taken during childhood reliably predict performance on national tests of educational achievement 5 years later (Deary, Strand, Smith, & Fernandes, 2007) and socioeconomic level at midlife (Foverskov et al., 2017).

? How meaningful are IQ scores?

Critics believe that scores on traditional intelligence tests are closely related to academic performance and to higher socioeconomic levels mostly because the tests were designed to reflect that kind of success. According to these critics, the tests overemphasize verbal ability, education, and Western culture. A few tests are designed to be culture-free, such as the Raven Progressive Matrices (Raven, 2003). These tests are mostly nonverbal, and the tasks require no experience with a particular culture (Figure 13.3). They have an obvious advantage for testing people from a very different culture or language background or with impaired understanding of language. Some researchers also believe that these tests give them a better representation of "pure" intelligence.



Description

Figure 13.3 Example of a Problem From Raven's Progressive Matrices. The task is to determine which of the eight patterns at the bottom completes the puzzle above. (The correct answer is eight.)

Source: From Clancy Blair, David Gamson, Steven Thorne, David Baker, "Rising mean IQ: Cognitive demand of mathematics education for young children, population exposure to formal schooling, and the neurobiology the prefrontal cortex." *Intelligence,* Volume 33, Issue 1, January–February 2005, pages 93–106, with permission from Elsevier.

Claiming that true intelligence is much more than what the tests measure, these critics often point to instances where practical intelligence or "street smarts" is greater than conventional intelligence. For example, as young Brazilian street vendors conducted their business, they were adept at performing calculations that they were unable to perform in a classroom setting (Carraher, Carraher, & Schliemman, 1985). In another study, expert racetrack gamblers used a highly complex algorithm involving seven variables to predict racetrack odds, but their performance was unrelated to their IQ; in fact, four of them had IQs in the low to mid-80s (Ceci & Liker, 1986). Robert Sternberg (2000) compared the scores that the presidential candidates George W. Bush, Al Gore, and Bill Bradley made on the verbal section of the Scholastic Aptitude Test (SAT) when they applied for college; the SAT has many items similar to those on conventional intelligence tests. Two of the candidates scored above average for college applicants but not markedly so, and one had a score that was below average. To Sternberg, their success raises questions about the narrowness of what intelligence tests measure.

Sternberg (1988) argues that intelligence does not exist in the sense we usually conceive of it but is "a cultural invention to account for the fact that some people are able to succeed in their environment better than others" (p. 71). Perhaps intelligence is, like the mind, just a convenient abstraction we invented to describe a group of processes. If so, we should not expect to find intelligence residing in a single brain location or even in a neatly defined network of brain structures. And to the extent we find processes or structures that are directly involved in intellectual ability, their activity might be only moderately correlated with scores on traditional intelligence tests.

The Structure of Intelligence

Another controversy that is critical to a biological understanding of intelligence is whether intelligence is a single capability or a collection of several independent abilities. Intelligence theorists tend to fall into one of two groups, *lumpers* or *splitters*. Lumpers claim that intelligence is a single, unitary capability, which is usually called the *general factor*, or simply *g*. General factor theorists admit that there are separate abilities that vary somewhat in strength in an individual, but they place much greater

weight on the underlying g factor. They point out that a person who is high in one cognitive skill is usually high in others, so they believe that a measure of g is adequate by itself to describe a person's intellectual ability. General intelligence is often assessed by the overall IQ score from a traditional intelligence test, such as the Wechsler Adult Intelligence Scale, whose 11 subtests measure more specific abilities. But many g theorists prefer to use tests like the Raven Progressive Matrices, because they emphasize reasoning and problem solving and are relatively freer of influence from specific abilities such as verbal skills.

Splitters, by contrast, hold that intelligence is made up of several mental abilities that are more or less independent of each other. Therefore, they are more interested in scores on the subtests of standard IQ tests or scores from tests of specific cognitive abilities. They may agree that there is a general factor, but they give more emphasis to separate abilities and to differences among them in an individual. An accurate description of a person's intelligence would require the scores on all the subtests of these abilities. These theorists point to cases of brain damage in which one capability is impaired without affecting others and to the savant's exceptional ability in a single area. H. M. (discussed in Chapter 12), for example, had an overall IQ of 110, but his Performance IQ was 123, his Verbal IQ was 103, and his Memory IQ was 73 (Corkin, Amaral, González, Johnson, & Hyman,, 1997). Splitters disagree with each other, though, on how many abilities there are; a review of intelligence tests identified more than 70 different abilities that can be measured by available tests (Carroll, 1993).

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- What do IQ scores tell us, and not tell us, about a person's capabilities?
- What difference does it make to our search for a biological basis for intelligence whether intelligence is a "real" entity or an invented concept?
- What is the lumper–splitter controversy?

THE BIOLOGICAL ORIGINS OF INTELLIGENCE

With this background, we are now ready to explore the origins of intelligence. Based on our introduction, we will avoid two popular assumptions—that intelligence tests are the only way to define intelligence and that intelligence is a single entity. Instead, we will consider performance and achievement as additional indicators of intelligence, and we will first examine the evidence of a biological basis for a general factor and then consider the relationship between brain structures and individual abilities.

The Brain and Intelligence

Is a more intelligent brain different in any identifiable way from other brains? Anyone asking this question would naturally wonder how Albert Einstein's brain was different from other people's. Fortunately, the famous scientist's brain was preserved, and it has been made available from time to time to neuroscientists (Figure 13.4). In cursory examinations, it turned out to be remarkably unremarkable. In fact, at 1,230 grams (g), it was 100 g under the weight for the average male of his age (Harrison, Freemantle, & Geddes, 2003). The number of neurons did not differ from normal, and studies have disagreed about whether the neurons were more densely packed or the cortex was thinner, perhaps because the samples were taken from different locations (B. Anderson & Harvey, 1996; Kigar, Witelson, Glezer, & Harvey, 1997). One study found a higher ratio of glial cells to neurons in the left parietal lobe (M. C. Diamond, Scheibel, Murphy, & Harvey, 1985). The comparison brains averaged 12 years younger than Einstein's at the time of death, and we know that glial cells continue proliferating throughout life (T. Hines, 1998), but the number of glial cells was not

elevated in Einstein's right parietal lobe or in either frontal sample. Each of Einstein's hemispheres was a full centimeter wider than those of control brains, due to larger parietal lobes (Witelson, Kigar, & Harvey, 1999), and there were intriguing variations in some of the parietal gyri (Falk, 2009). These anomalies are interesting because the parietal lobes are involved in mathematical ability and visual-spatial processing, and Einstein reported that he performed his mathematical thinking not in words but in images. Remember, though, that in Chapter 12, we saw that London taxi drivers have enlarged posterior hippocampi, and no one would suggest that large hippocampi explain why they became taxi drivers. In fact, a later follow-up study found that drivers who qualified at the end of their training increased in hippocampal volume, but drivers who failed to qualify did not (Woollett & Maguire, 2011). Whether Einstein's large parietal lobes or intense mathematical activity came first is uncertain (assuming they are related).

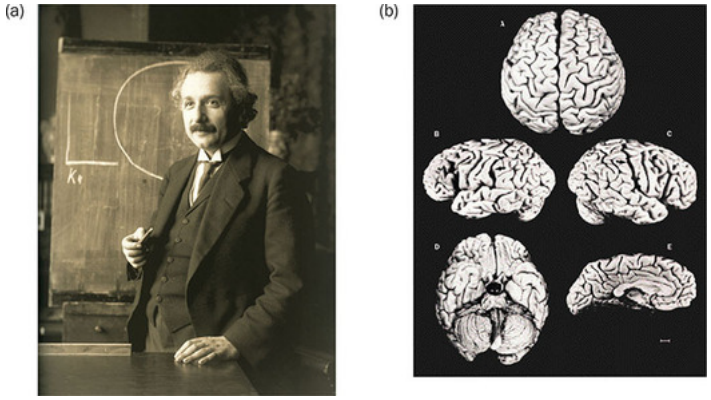


Figure 13.4 Albert Einstein and His Brain.
The brain of the genius looks just like yours; it took careful study to find differences.

Sources: (a) Wikimedia Commons/Ferdinand Schmutzer. (b) Figure 1. "The Exceptional Brain of Albert Einstein, " by Witelson, S. F., Kigar, D. L., & Harvey, T., *The Lancet*, 353(9170), 2149–2153.

? How are intelligent brains different?

It is interesting that the strongest finding in the examination of Einstein's brain seems to be related to a specific ability rather than to overall intelligence. British researcher John Duncan and his colleagues (2000) sought the location of general intelligence in the brains of more ordinary folk. They used tasks that required reasoning and that are known to correlate with general intelligence more than with any specific ability. Although verbal and spatial tasks had different patterns of activation, prefrontal activation was common to both tasks; the authors concluded that general intelligence may be located there. But general intelligence is likely more complex than what happens in one area of the brain. A team of researchers scanned the brains of 241 individuals with brain damage and correlated the location of their lesions with their scores on a set of intelligence subtests chosen to measure g (Gläscher et al., 2010). They concluded that g requires a distributed system, a network that spans the frontal, parietal, and temporal lobes (Figure 13.5). They suggested that g involves the brain's ability to pull together different kinds of processing, such as visual-spatial processing and working memory. The ability to integrate these functions depends on the quality of connections between the areas, which is highly heritable, up to 84% in some parts of the brain (Chiang et al., 2009).

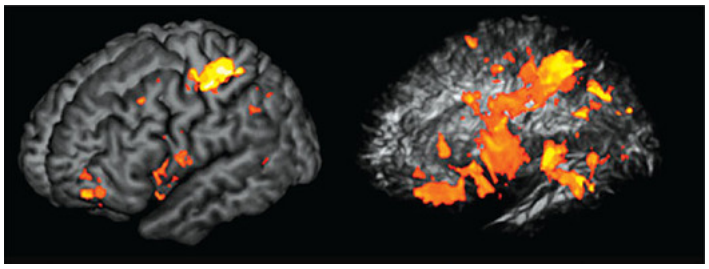


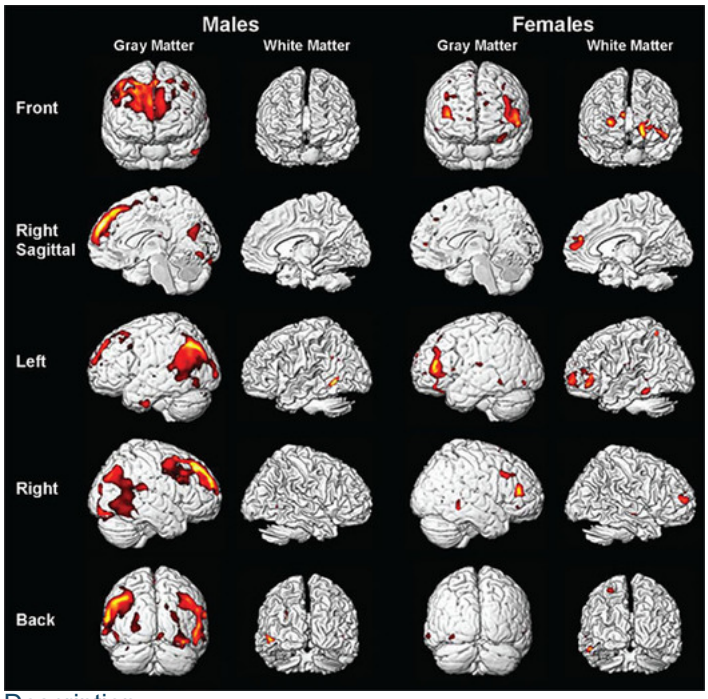
Figure 13.5 Brain Areas Involved in General Intelligence.
A view of the cortical surface (left) and subcortical areas (right) shows a g-related network extending throughout much of the brain.

Source: From "Distributed Neural System for General Intelligence Revealed by Lesion Mapping," by J. Gläscher et al., 2010, *Proceedings of the National Academy of Sciences*, *90,* pp. 4705–4709.

Brain Size

Popular wisdom is that smart people have bigger brains, and that is true—to an extent, at least. A meta-analysis of 88 studies including more than 8,000 individuals found a correlation between intelligence and brain size of .24 (Pietschnig, Penke, Wicherts, Zeiler, & Voracek, 2015). This means that variations in brain size account for only about 6% (0.24^2) of people's differences in intelligence. Even this small amount of relationship breaks down if we try to apply it across species; elephants have much larger brains, and not many people think elephants are smarter than we are. In fact, it has been difficult to explain differences in intelligence across species. Various proposals have come into vogue and then been abandoned; the number of neurons in the brain, for example, again favors elephants, and the ratio of brain weight to body weight indicates that the marmoset monkey should be smarter than humans. After meticulously counting neurons in numerous animal brains, Suzana Herculano-Houzel (2017) concluded that the best correlate of cognitive ability across species is the absolute number of neurons in the cerebral cortex. She suggests that the number of neurons in the prefrontal cortex, which is so important in learning, language, and other higher-order behaviors, would probably be an even better measure, but she hasn't collected the data yet.

Now back to what accounts for differences in intelligence among our own kind. Not surprisingly, the amount of gray matter is somewhat predictive of intelligence, with a correlation of .37; white matter volume similarly has a correlation of .26 (Narr et al., 2007). This is where we begin to see sex differences. If you look at Figure 13.6, you will see that IQ varies with gray matter volume in more brain areas in males and with white matter volume in more areas in females (Narr et al., 2007). These results tell us that cognitive performance depends on a broadly distributed network. But it also suggests that this is a dynamic network that accommodates the different strategies males and females adopt to achieve comparable results (Pietschnig et al., 2015).



Description

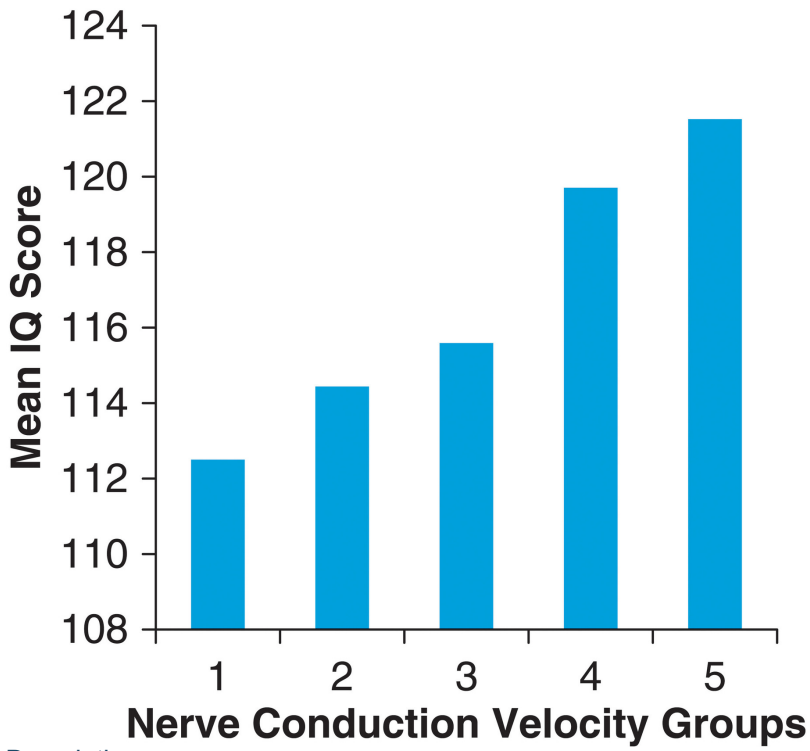
Figure 13.6 Correlations Between Gray Matter and White Matter Volumes and IQ. Notice that gray matter volume is correlated with IQ in more areas in men than in women, and white matter volume is correlated with IQ in more locations in women than in men. (Lighter colors indicate stronger relationships.)

Source: Montreal Neurological Institute.

But knowing gray and white matter volumes doesn't add much to our ability to predict intelligence, because they are not independent of brain size. This tells us that we must look further for additional roots of intelligence.

Processing Speed and Efficiency

All the gray matter in the world is useless without the white matter connections that make up the brain's communication network. The quality of this communication depends in part on processing speed, and a major contributor to processing speed is the shortness or directness of the connections, or *white matter efficiency*. White matter efficiency is one of the brain characteristics that is highly related to intelligence and educational achievement (Bathelt, Scerif, Nobre, & Astle, 2019). Another contributor to processing speed is the speed of conduction itself. In 1883, before there were any intelligence tests, Sir Francis Galton attempted to relate measures of intellectual achievement such as course grades and occupational status to people's reaction times. There is some relationship with reaction time, but more so with its major determiner, *nerve conduction velocity* (Figure 13.7; T. E. Reed & Jensen, 1992). Nerve conduction velocity depends in turn on *white matter integrity*, which is the ability of the axon wall and its myelin insulation to prevent diffusion of fluid out of the axon. White matter integrity also is correlated with intelligence and explains 10% of its variance (Penke et al., 2012). IQ varies among individuals with the degree of myelination (Willerman, Schultz, Rutledge, & Bigler, 1994). In addition, myelination, speed of information processing, and intelligence all follow a curvilinear time path, increasing from childhood to maturity and then declining in old age (Bennett & Madden, 2014).

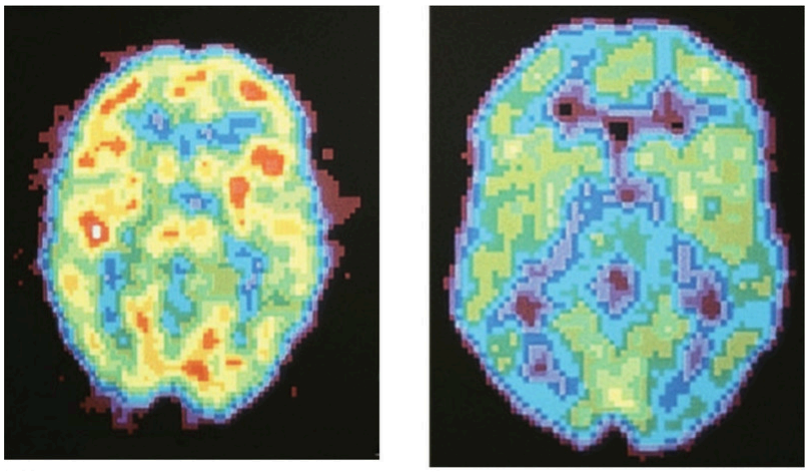


Description

Figure 13.7 Relationship Between IQ Scores and Nerve Conduction Velocity. The research participants were divided into five groups according to their nerve conduction velocity. Group 1 had the lowest nerve conduction velocity and Group 5 the highest. Nerve conduction velocity was calculated as elapsed time between a stimulus and the occurrence of the evoked potential divided by the distance between the eyes and the back of the head.

Source: Adapted from "Conduction Velocity in a Brain Nerve Pathway of Normal Adults Correlates With Intelligence Level," by T. E. Reed and A. R. Jensen, *Intelligence, 16*, pp. 259–272. Copyright 1992, with permission from Elsevier Science.

A surprising finding in studies of the brain's role in intelligence is that individuals who are higher in IQ use less brain energy when they are solving a problem. This was indicated by a lower rate of glucose metabolism in the brain during a challenging task, playing the computer game Tetris (Haier, Siegel, Tang, Abel, & Buchsbaum, 1992). And as you can see in Figure 13.8, individuals with mild intellectual disability (IQs between 50 and 70) require 20% more neural activity to perform an attention-demanding task than do individuals with IQs of 115 or higher (Haier et al., 1995). You might think the more intelligent brain would be the more active one during a task, but remember that we are talking about efficiency.



(a) (b)

Figure 13.8 Greater Efficiency in the More Intelligent Brain.
During an attention-demanding task, PET scans showed 20% more activity (indicated by more reds and yellows) in (a) the brain of an individual with intellectual disability than in (b) the brain of a person with above-average IQ.

Source: From "Brain Size and Cerebral Glucose Metabolic Rate in Nonspecific Mental Retardation and Down Syndrome," by R. J. Haier et al., 1995, *Intelligence*, *20,* pp. 191–210.

Specific Abilities and General Intelligence

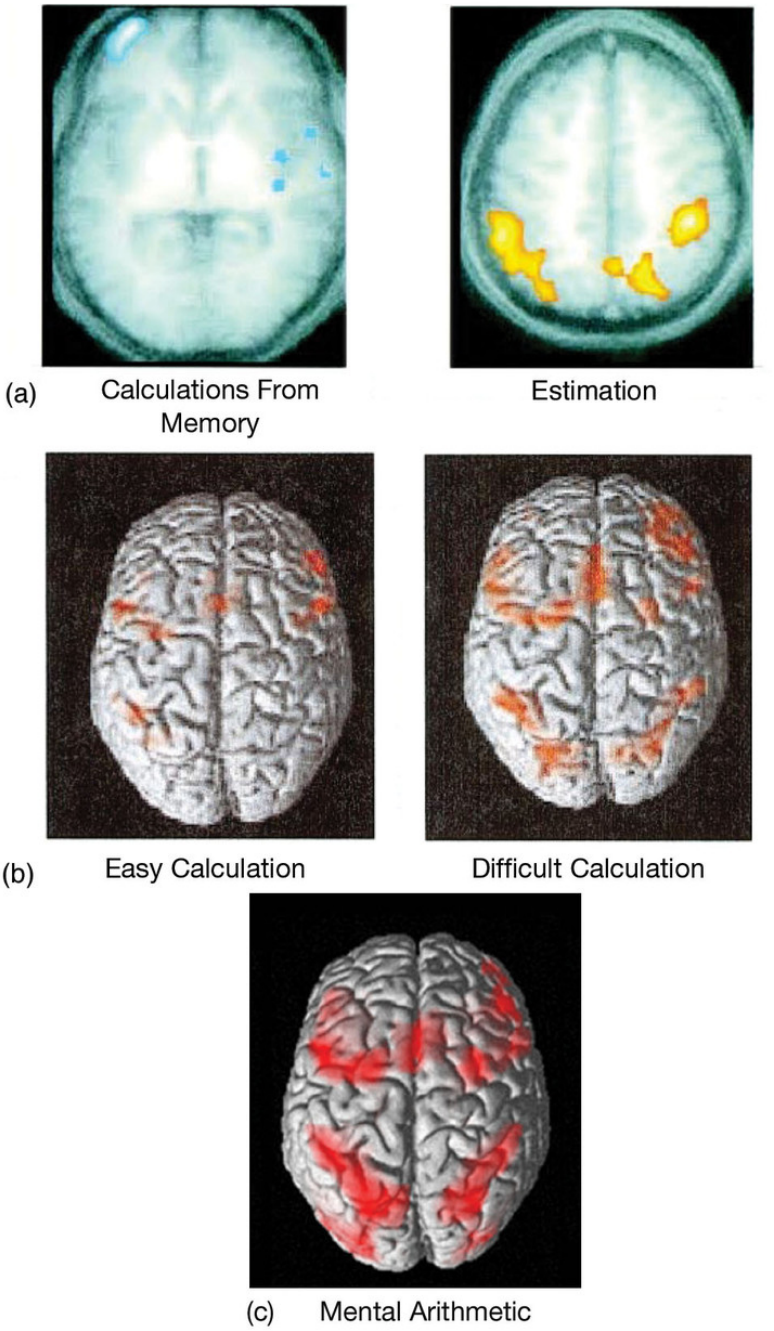
We said earlier that the idea of general intelligence easily accommodated individual components, known as *specific factors*. Its original proponent, the English psychologist Charles Spearman, came up with the theory after he used the very powerful statistical method he invented, called *factor analysis*, to analyze a multitude of tests of mental ability. The procedure involves giving a group of people several tests that measure cognitive abilities. Then correlations are calculated among all combinations of the tests to locate "clusters" of abilities that are more closely related with each other than with the others. The strong correlation across most of the measures suggested that mathematical skills, verbal skills, artistic ability, reasoning skills, and so on were all influenced by a common factor, general intelligence (Spearman, 1904). But factor analysis has also been useful in identifying clusters of more specific abilities. Three capabilities have emerged frequently as major components of intelligence: *linguistic*, *logical-mathematical*, and *spatial* (Jensen, 1998).

Several authors have argued that each of the cognitive abilities depends on a complex network or module in the brain that has evolved in ways that support that function. Some go further, suggesting that some capabilities, such as mathematics and language, are hardwired into the brain (Dehaene, 1997; Pinker, 1994). We have already seen examples of modular functions in earlier chapters; for example, the language (linguistic) module is made up of a network of structures located mainly in the left frontal and temporal lobes (see Chapter 9). And in Chapter 7, we saw evidence that a parietal lobe "spatial module" might account for men's higher performance on the Mental Rotations Test.

? Are there separate components of intelligence?

Mathematical ability depends on the prefrontal cortex and the parietal cortex; which areas are activated and how much depends on the kind of task and the level of difficulty. The left prefrontal cortex is most active when an individual performs calculations from memory, such as 2 × 4 and 2 + 4; the area is probably the storage site of arithmetic facts. Both parietal areas come into play during estimation of values (Figure 13.9a; Dehaene, Spelke, Pinel, Stanescu, & Tsivkin, 1999); this makes sense,

because visual-spatial representations of quantity, such as finger counting and the "number line," are an almost universal stage in learning exact calculation. Calculation recruits both left and right prefrontal areas and both parietal cortices; activation increases further in the parietal lobes with increasing difficulty (incorporating an additional step to the calculation) and in the prefrontal areas as speed demands increase (Figure 13.9b; Menon, Rivera, White, Glover, & Reiss, 2000). Studies of brain damage support these conclusions. Individuals with damage to the left frontal language area can arrange numbers in rank order and estimate results, but they cannot perform precise calculations; those with parietal damage are impaired in the opposite direction (Butterworth, 1999; Dehaene & Cohen, 1997). Katherine Keller and Vinod Menon (2009) also observed frontal and parietal activation as their subjects did multistep mental arithmetic, but they found activation in the occipital areas as well, demonstrating that people recruit additional resources as needed, in this case, visualization (Figure 13.9c). Four clusters in the right hemisphere were more activated in men than in women, but this did not translate to greater calculation accuracy. So although brain differences sometimes result in performance differences, once again, we see evidence of males and females using different brain strategies to achieve comparable results.



Description

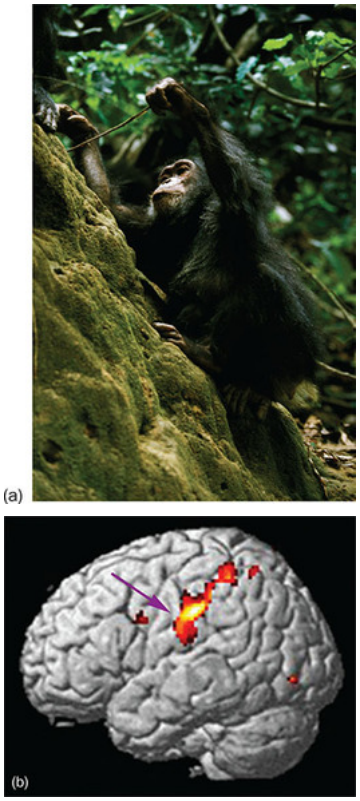
Figure 13.9 Brain Locations Involved in Mathematical Performance.
(a) Calculations from memory (such as 2 × 4) activate primarily left prefrontal cortex; estimation involves both parietal cortices. (b) Non-rote calculation involves all four areas, and activation increases with difficulty (for example, 5 – 2 versus 6 + 3 – 5). (c) Activation of all four areas plus occipital areas during multistep mental arithmetic.

Sources: (a) From "Sources of Mathematical Thinking: Behavioral and Brain-Imaging Evidence," by S. Dehaene, E. Spelke, P. Pinel, R. Stanescu, & S. Tsivkin, 1999, *Science, 284*, pp. 970–973. Reprinted with permission of AAAS. (b) From "Dissociating Prefrontal and Parietal Cortex Activation During Arithmetic Processing," by V. Menon, S. M. Rivera, C. D. White, G. H. Glover, and A. L. Reiss, 2000, *NeuroImage*, *12,* pp. 357–365.

Obviously, neither of these areas is dedicated exclusively to numeric functions. This is consistent with the suggestion in Chapter 9 that the language areas may simply use processing strategies that make them particularly suited to the demands of the task, rather than being dedicated to language processing. However, Wynn (1998) argues that the brain has a specialized mechanism for numbers by pointing to evidence that even infants and lower primates seem to have an inborn ability to estimate quantities. The infants she studied saw two objects placed one at a time behind a screen. They acted surprised—which means that they looked for a longer time—when the screen was removed to reveal three objects or only one object instead of the expected two (Wynn, 1992). Rhesus monkeys tested in the wild responded to the task the same way (Hauser, MacNeilage, & Ware, 1996). Monkeys can rank-order groups of objects that differ in number by touching their images on a computer monitor in the correct order (Brannon & Terrace, 1998), and chimpanzees have learned to do the same with numerals (Kawai & Matsuzawa, 2000). This reminds us that we shouldn't think of intelligence as a uniquely human domain, which is the topic of A Further Look.

A Further Look:

We Aren't the Only Tool Users



A chimp dines on termites "fished" from their mound with a stick.

Auscape / Contributor / Getty Images

Source: From "The Representation of Tool Use in Humans and Monkeys: Common and Uniquely Human Features," by R. Peeters et al., 2009, *Journal of Neuroscience, 29*, pp. 11523–11539.

Humans have been fascinated with how intelligent animals' behavior can seem. Termites build earthen mounds that are so well ventilated they stay cool under the African sun. Dolphins cooperate with each other to herd schools of fish into their pod mates' waiting mouths. As discussed in Chapter 9, Kanzi communicates with

symbols, Alex mastered simple concepts, and monkeys and chimpanzees can "count."

Especially intriguing is the concept of tool use. Chimpanzees have long been known to "fish" for termites by punching a hole in the nest and inserting a small green twig that the termites climb onto in defense of the nest, only to be slurped up by the chimp (Figure a; Holden, 2004b). Congo chimps add a unique twist: They fray the end of the twig, enabling them to pick up 20 times as many termites (C. Sanz, Cali, & Morgan, 2009). New Caledonian and Hawaiian crows cut and shape twigs and use them to extract food from crevices, and they have been observed to spontaneously shape wire into hooks to retrieve food (Rutz et al., 2016; Weir, Chappell, & Kacelnik, 2002). Visayan warty pigs have even been observed using sticks and pieces of bark to dig a pit for a nest (Dell'Amore, 2019).

But Santino, a chimp in a Swedish zoo (Osvath, 2009), may demonstrate the greatest ingenuity. Santino occasionally threw stones at visitors, but zookeepers weren't concerned because there was so little ammunition on his island. Then stone throwing increased dramatically, so a caretaker watched to figure out where the stones were coming from. Each morning, Santino retrieved stones from the moat and placed them strategically for launching at the visitors. He was also seen dislodging chunks of concrete from a wall, after first tapping where there were cracks and listening for the hollow sound that meant a piece was loose enough to be removed.

So what do these research observations tell us? First, animals are more intelligent than we've given them credit for. Second, some of our capabilities aren't unique, after all. But we also have a chance to discover where we are truly different. For example, watching someone retrieve an object with the hand activates mirror neurons that are similarly located in humans and in monkeys (Peeters et al., 2009). However, when a human sees the object being retrieved with a tool, an additional area is activated in the anterior parietal lobe (Figure b); yet no such area for tool use showed up in the monkeys, even the ones that were trained for 3 to 6 weeks to use the same tools. Apparently we have developed some additional specialized structures, either through evolution or individual experience.

So far we have been talking about moderately localized networks specialized for handling specific abilities. According to the Parieto-Frontal Integration Theory, general intelligence depends on how well parietal and frontal brain networks integrate with each other (R. E. Jung & Haier, 2007). After reviewing 37 imaging studies, Jung and Haier concluded that parietal areas abstract sensory information and integrate it, then these areas interact with frontal areas to evaluate the information. Subsequent research has confirmed these areas as central to intelligence and indicated that the parietal cortex acts as the main hub (Langer et al., 2012). These networks are not necessarily rigid, however, but can be altered by changing their functional connectivity. According to the Network Neuroscience Theory, differences in general intelligence are related to the brain's ability to reconfigure networks on the fly in order to allow cognitive flexibility and adaptive problem solving (Barbey, 2018).

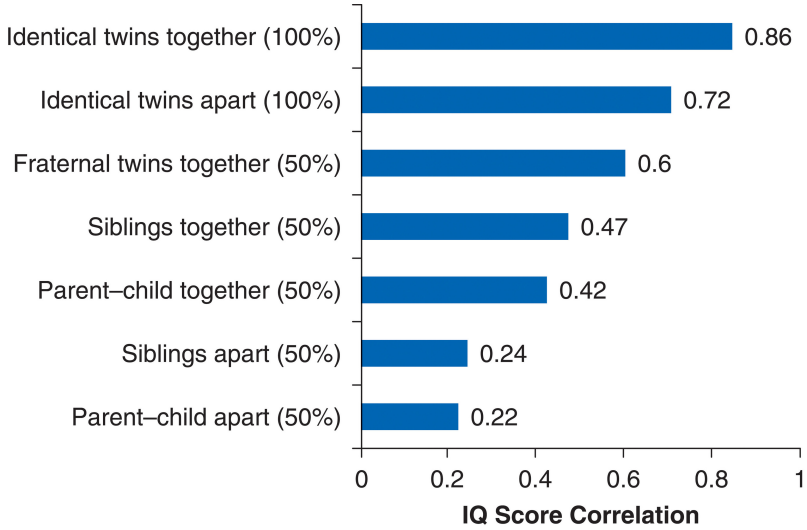
Heredity and Environment

We saw in Chapter 1 that intelligence is the most investigated of the genetically influenced behaviors. Our understanding of the genetic underpinnings of intelligence hardly lives up to the amount of effort, however; this is because intelligence is so complex and poorly understood itself and because many genes are involved. In addition, environment accounts for half of the differences among us in intelligence, yet the environmental influences have themselves not been clearly identified (Plomin, 1990).

Heritability of Intelligence

Figure 13.10 shows the IQ correlations among relatives, averaged from many studies and several thousand people. You can see that IQ is more similar in people who are

more closely related (T. J. Bouchard & McGue, 1981). Separating family members early in life does not eliminate the correlation; in fact, identical twins reared apart are still more similar in IQ than are fraternal twins reared together. Heritability of intelligence averages about 50%. We have to give an average, because heritability *increases* with age, from 41% in childhood to 55% in adolescence and 66% in adulthood (Haworth et al., 2009). Intuition tells us that environment should progressively overtake genetic effects as siblings go their separate ways and their experiences diverge. But Briley and Tucker-Drob (2013) suggest that the genes that influence intelligence also influence the individual's choices of environment and experience, which narrows the environment and reduces its relative influence.



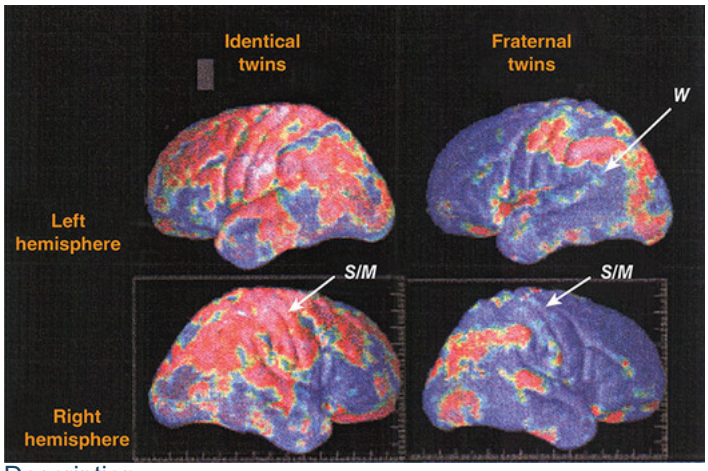
Description

Figure 13.10 Correlations of IQ Scores Among Relatives.
Percentages indicate the degree of genetic relatedness. "Together" and "apart" refer to whether related children are raised in the same household.

Source: Data from "Familial Studies of Intelligence: A Review," by T. J. Bouchard and M. McGue, 1981, *Science*, *212*, pp. 1055–1059.

? Which is more important, heredity or environment?

Researchers have documented genetic influence on several of the functions that contribute to intelligence, including working memory, processing speed, and reaction time in making a choice (Ando, Ono, & Wright, 2001; Luciano et al., 2001; Posthuma, de Geus, & Boomsma, 2001). Heredity also accounts for most of the differences among individuals in the major structural contributors to intelligence; estimated heritabilities in one twin study were 90% for brain volume, 82% for gray matter, and 88% for white matter (Figure 13.11; Baaré et al., 2001). Specific genes have been identified that link intelligence with brain size, cortical thickness, and integrity of major pathways (Chiang et al., 2012; Desrivières et al., 2014; J. L. Stein et al., 2012).



Description

Figure 13.11 Genetic Control of Gray Matter Volume in Identical and Fraternal Twins. Red indicates areas where the correlation between twins in gray matter was most significant; green indicates lesser correlation; and blue, no statistically detectable relationship. Notice the markedly greater similarity (greater abundance of red) between identical twins. (W indicates Wernicke's area and S/M the somatosensory and motor areas.)

Source: Reprinted by permission from Macmillan Publishers Ltd. From "Genetic Influences on Brain Structure," by Paul M. Thompson et al., 2001, *Nature Neuroscience, 4*(12), pp. 1253–1258. © 2001 Nature Publishing Group.

But the effects of individual genes are so small that detecting them with reliability will require sample sizes of 250,000 or more; in addition, accounting for the heritability of intelligence is expected to require identification of 10,000 DNA variations (Plomin & von Stumm, 2018). A major boost in that regard came when researchers started using educational attainment as a proxy for intelligence; "years of education" is one of the questions asked in almost every genome-wide association study (GWAS). A GWAS with more than 1 million participants has identified 1,000 DNA associations, which together account for 20% of the 50% total heritability.

The Genetic Controversy

The conclusion that intelligence is highly heritable has not been greeted with unquestioning acceptance. The idea is controversial on a variety of fronts; these controversies illustrate both the pervasive misunderstanding of genetic influence and the difficulty in resolving questions of heredity. Critics fear that inheritance of intelligence implies that intelligence is inborn and unchangeable (Weinberg, 1989). Nothing could be further from the truth, however; as Weinberg points out, genes do not fix behavior but set a range within which the person may vary. By way of illustration, height is about 90% heritable (Plomin, 1990), yet the average height has increased dramatically over the past few decades, due to improved nutrition. Similarly, IQ scores increased in 14 countries at the rate of 5 to 25 points over just a generation (termed *the Flynn effect*; Flynn, 1987). (These increases are "hidden" because each time an IQ test is revised, it is restandardized to an average of 100 points.) Such rapid increases cannot be due to genetic changes. However, we know that the world is a much more stimulating, information-filled place and education has changed dramatically, and as Flynn points out, in 1900, the median year of schooling was 6 years, compared with 13 years now, and schools taught by memorization and recitation (Flynn, te Nijenhuis, & Metzen, 2014). Research indicates that several countries are experiencing a slowdown or even a reversal of the Flynn effect. By comparing IQs within and between families over a period of three decades, Norwegian researchers concluded that an increase and then an equal decrease in

scores in that country was due to within-family environmental influences (Bratsberg & Rogeberg, 2018).

Some researchers argue that the correlation of IQ among relatives does not mean that intelligence is inherited. They suggest, for example, that identical twins' similarity in appearance and personality lead others to treat them similarly, even when they are reared apart, and this similar treatment results in similar intellectual development. Although physical features and behavior do affect how others react to a child, there is little evidence that these responses in turn influence intelligence. To test this possibility, researchers compared the IQs of twins who had been either correctly or incorrectly perceived by their parents as fraternal or identical. If similar environmental treatment accounts for IQ similarity, then the parents' perception of their twins' classification should be more important than the twins' actual genetic classification. Instead, the studies showed that only the true genetic relationship influenced IQ similarity in the twins, not the parents' perception (Scarr & Carter-Saltzman, 1982).

In another controversy, a debate has raged since the 1930s over whether IQ differences between ethnic groups are genetically based. The question is not whether the ethnic groups differ in IQ scores but how much the differences are due to heredity and to environment. Arthur Jensen (1969) argued that environment and socioeconomic differences are inadequate to account for the observed IQ differences among groups. He and Philippe Rushton cited studies indicating that IQ differences are consistent around the world, with East Asians averaging 106 points, whether in the United States or in Asia, Whites about 100, and African Americans at 85 and sub-Saharan Africans around 70 (J. P. Rushton & Jensen, 2005). In addition, they say that the IQ gaps correspond to differences in brain size. Their position has practical as well as theoretical implications. For example, extreme hereditarians believe that intervention efforts like Head Start not only do not work but also cannot work.

Other intelligence researchers countered that Jensen and Rushton ignored or misinterpreted the most relevant data (Nisbett, 2005). For example, African Americans with more African ancestry scored as high on cognitive tests as those with mixed ancestry (Scarr, Pakstis, Katz, & Barker, 1977). Another study suggests that socioeconomic class is more important than ethnic origin; it found that IQ runs about 20 to 30 points lower in the lowest social classes than in the highest social classes (Locurto, 1991). Higher intelligence test results are not always found for Asians (Naglieri & Ronning, 2000), and their higher academic achievement is typically attributed to cultural and motivational differences (Dandy & Nettelbeck, 2002). A task force appointed by the American Psychological Association to study the intelligence debate concluded that there is not much direct evidence regarding the genetic hypothesis of IQ differences between African Americans and Whites, and what little there is does not support the hypothesis (Neisser et al., 1996).

Environmental Effects

Most intelligence researchers agree that intelligence is the result of the joint contributions of genes and environment; it has even been said that intelligence is 100% hereditary and 100% environmental, because both are necessary. However, it has been more difficult than expected to identify just which environmental conditions influence intelligence, other than those that cause brain damage. We will give environmental influences more attention here than usual because intelligence is a good arena for illustrating the difficulties in sorting out heredity from environment. One problem is similar to the one we have encountered in identifying specific genes: The environmental influences are many and, for the most part, individually weak (Jensen, 1981). Even a twin study that looked at major environmental events, such as severe infant and childhood illness, failed to find an effect (Loehlin & Nichols, 1976). A second problem is that environmental influences are often hopelessly confounded with genetic effects. For example, family conditions such as socioeconomic level and parental education are moderately related to the offspring's intelligence (T. J. Bouchard & Segal, 1985), but these characteristics also reflect the parents' genetic makeup, which they pass on to their children.

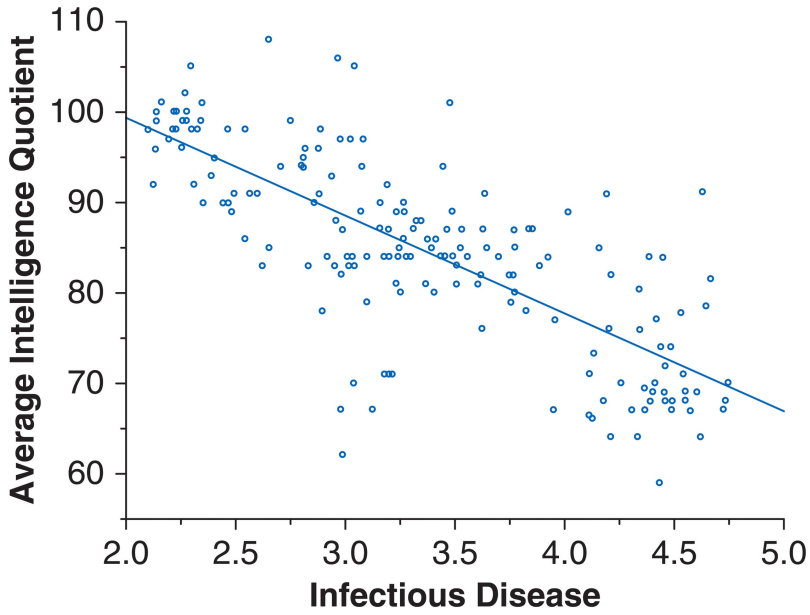
The best way to demonstrate environmental influences is by environmental intervention. Although the Head Start program has produced long-term benefits in mathematics, educational attainment, and career accomplishments, the average increase of 7.42 IQ points compared with controls eventually disappears. The Abecedarian Project, which began at birth, produced IQ gains that were as strong 10 years later as those in the Head Start program after 2 years (Ramey et al., 2000). Apparently, intervention must occur at an earlier age; now the Early Head Start program takes children from birth through age 5. A more dramatic intervention is adoption, because it alters the child's entire environment (Scarr & Weinberg, 1976). Adopted children's IQs are more highly correlated with the intelligence of their biological parents than with the intelligence of their adoptive parents (Scarr & Weinberg; Turkheimer, 1991), but this does not mean that the children's IQs do not go up or down according to the adoptive environment. When African American children were adopted from impoverished homes into middle-class homes, by the age of 6, their IQs had increased from the 90-point average for African American children in the geographic area to 106. The beneficial effects persisted a decade later (Scarr & Weinberg, 1976; Weinberg, Scarr, & Waldman, 1992).

Does this mean there was no genetic effect at all? No. In fact, the correlation between the children's IQs and their biological parents' educational levels (used in the absence of IQ scores) *increased* over the 10-year follow-up period, while correlations with their adoptive parents' educational levels *decreased* (Weinberg et al., 1992). It may puzzle you how the children's IQs could be correlated with their biological parents' intelligence if the children's IQs had moved into the adoptive parents' range. Although we usually think that correlation indicates similarity within pairs of scores (e.g., a parent's and a child's IQs), this is not necessarily the implication; rather, it means that the scores have similar rank orders in their groups. In other words, the parent with the highest IQ has the child with the highest IQ, the parent with the second-highest IQ has the child with the second-highest IQ, and so on. Now move the children into a new household and raise each child's IQ by 10 points; the biological parent with the highest IQ still has the child with the highest IQ, and the parent with the second-highest IQ…. You get the point. The correlation tells us that the children's IQs are still tied to their biological parents' intelligence, as if by an elastic string that can stretch but nevertheless affects *how much* the IQ can change; that elastic string in this case is the influence of genes.

Though it has been difficult to identify specific environmental influences that increase intelligence, we have had some success identifying influences that have a deleterious effect. One example is prenatal exposure to pesticides. In an agricultural community in California, children whose mothers had high levels of organophosphate pesticide residue in their blood during pregnancy averaged 7.0 IQ points lower, compared with children of mothers with the lowest residue measures (M. F. Bouchard et al., 2011). The exposed children also scored lower on tests of working memory, processing speed, verbal comprehension, and perceptual reasoning. Similarly, children with the highest levels of prenatal exposure to chlorpyrifos scored 2.7 points lower in IQ and 5.3 points lower on a test of working memory (Rauch et al., 2011). Until it was banned for indoor use in 2001, chlorpyrifos was one of the most widely used insecticides for household pest control; in 2018, a federal court ordered the Environmental Protection Agency (EPA) to ban agricultural use as well (Wallace, 2018).

Although childhood illness in general is not a predictor of later intelligence, infection does seem to be important. A study in a north Manhattan, New York, community found that people with multiple risk-associated pathogens also had lower cognitive ability (Katan et al., 2013). In a Danish study, individuals who had been hospitalized once for infection had a 1.76-point lower IQ than the average, and those with five or more hospital contacts scored 9.44 points lower (Benros et al., 2015). Researchers at the University of New Mexico concluded that the level of infectious diseases is the best predictor of national differences in intelligence (Eppig, Fincher, & Thornhill, 2010). After controlling for confounding variables, including education, climate, and economy, the correlation between national average IQ and infectious disease ranged from –.76 to –.82, depending on the method of estimating intelligence (Figure 13.12). Not only might disease prevalence partly account for racial differences in intelligence; the researchers also believe that reduction in the incidence of infectious diseases explains some of the IQ increase seen in the Flynn effect. The burden of fighting off

infections during childhood may rob the body of energy needed for normal brain development, but there also is evidence that the immune response in the brain impairs cognitive functioning, for example, by impairing brain plasticity and learning (Benros et al., 2015; M. Zhou et al., 2016).



Description

Figure 13.12 Worldwide Relationship Between Intelligence and Infectious Disease. Although the relationship is not perfect (in which all the dots would fall on the line), you can see that high IQ scores are associated with low levels of infection and low IQ scores are associated with high levels of infection.

Source: Adapted from "Parasite Prevalence and the Worldwide Distribution of Cognitive Ability," by C. Eppig, C. L. Fincher, and R. Thornhill, 2010, *Proceedings of the Royal Society B: Biological Sciences, 277* (1701), pp. 3801–3808.

We want to understand the antecedents of intelligence to enhance cognitive functioning and prevent the disorders that diminish it. We have already seen in Chapter 12 that this is a daunting challenge in the case of Alzheimer's disease, and A Further Look reveals that enhancing performance in normally functioning individuals is not so easy, either.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- What brain characteristics and structures contribute to general intelligence and its component abilities?
- Suppose you read a quote from a researcher that "intelligence is not a matter of a place in the brain but how well the brain does its job." Explain why someone would say this.
- What are the relative contributions of heredity and environment to intelligence? Why is it so difficult to identify the genetic influences? The environmental influences?

- How can adopted children's IQs increase into the range of their adoptive homes and yet be more highly correlated with their parents' intelligence? (*Hint:* Draw a diagram, with made-up IQ scores of children from several families.)

DEFICIENCIES AND DISORDERS OF INTELLIGENCE

Intelligence is as fragile as it is complex. Accordingly, the list of conditions that can impair intelligence is impressively, or depressingly, long. To give you a feel for the problems that can occur in this most revered of our assets, we will add a few thoughts to what we have already covered in Chapter 12 on aging, take a brief look at intellectual disability, then spend more time on autism in recognition of its half-century-long challenge to neuroscientists' investigative skills, and finish with attention-deficit/hyperactivity disorder.

Effects of Aging on Intelligence

In Chapter 12, we discussed the most widely known cognitive disorder of aging, Alzheimer's disease. Here, we will limit our attention to normal declines in cognitive abilities that are associated with aging. One source of normal decline is the reduced activity of numerous genes involved in long-term potentiation and memory storage due to age-related damage (T. Lu et al., 2004). Genes involved in synaptic functioning and plasticity, including those responsible for glutamate and GABA receptors and for synaptic vesicle release and recycling, are particularly affected.

A Further Look:

Enhancing Intelligence and Cognitive Performance

Source: iStock/picmax13.

Most of us feel the need for a bit of an edge as we deal with a demanding world. Drugs have long been the go-to solution; 34% of college students, for example, reported using stimulants ordinarily prescribed for attention-deficit/hyperactivity disorder (DeSantis, Webb, & Noar, 2008). The benefits of these drugs are modest, and the drugs can impair some types of cognitive functioning while they are enhancing others (Husain & Mehta, 2011). Manipulating genes might seem an alternative, but remember that the known genes have a very small individual influence. Neuroscientists have created mutant strains of mice that were smarter at one task or another, but these mice also had their problems. One strain was overly fearful, and another solved some problems well but struggled with simpler ones ("Small, Furry … and Smart," 2009).

Faced with these realities, researchers have sought more benign strategies. They have reported long-term improvement in solving mathematical problems following electrical stimulation to the scalp over the prefrontal cortex (Snowball et al., 2013) and demonstrated cognitive gains after subjects played video games that required extensive use of working memory (Anguera et al., 2013; Jaeggi, Buschkuehl, Jonides, & Shah, 2011). Furthermore, working memory training increased functional connectivity in the frontal-parietal networks (Jolles, van Buchem, Crone, & Rombouts,

2013; Mackey, Singley, & Bunge, 2013). Given these successes, some researchers have suggested the better question is not whether the techniques work but which training regimens produce the best real-life benefits (Jaeggi et al., 2011).

In the previous chapter, we saw that cognitive performance in the elderly can be improved by flavonoids in the diet and by computerized training. On the other end of the age spectrum, we're reminded of the importance of early stimulation. Psychologists visited the homes of Jamaican children ages 9 to 24 months who were stunted in growth (bottom 5th percentile for height; Gertler et al., 2014). Researchers played with the children weekly, provided books and toys, and taught the mothers better ways to interact with their children. Compared to control children, those who received early stimulation had better grades and higher IQs, showed less depression, and got into fewer fights; later in adulthood, they had 25% higher earnings.

The bottom line is that there is no magic pill to increase intelligence; the most promising approaches appear to be very basic—early stimulation, adequate diet, and practice, practice, practice.

? How much capability is lost by the elderly?

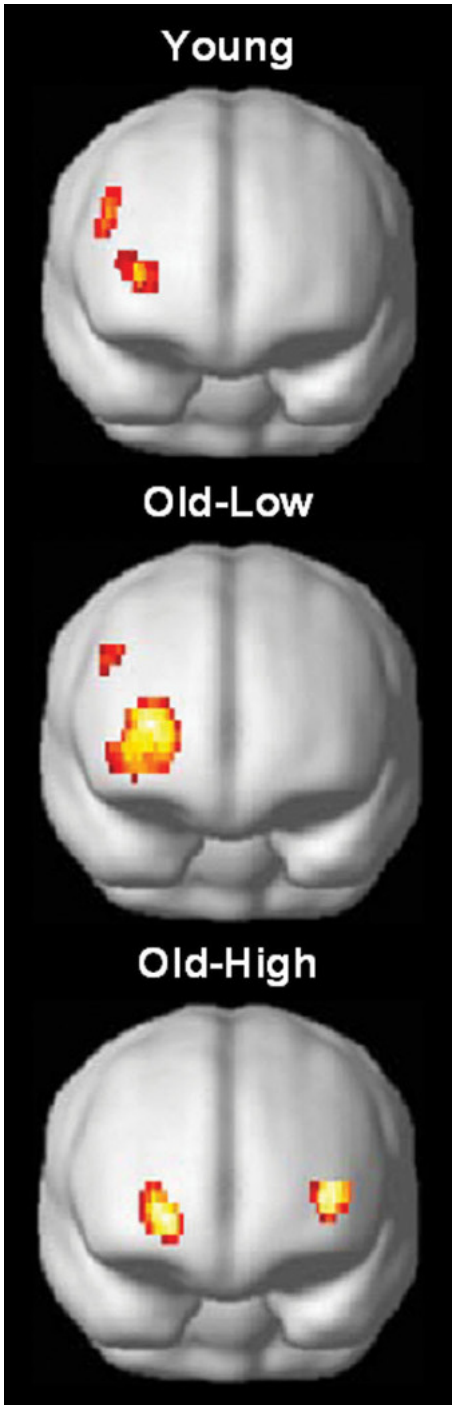
Although intelligence and cognitive abilities do typically decline with age, the amount of loss has been overestimated. One reason is that people are often tested on rather meaningless tasks, such as memorizing lists of words; when the elderly are tested on meaningful material, the decline is moderate (Kausler, 1985). Another reason for the overestimation is that early studies were *cross-sectional*, comparing people at one age with different people at another age; you have already seen that more recent generations have an IQ test performance advantage over people from previous generations. When the comparison is done *longitudinally*—by following the same people through the aging process—the amount of loss diminishes (Schaie, 1994). Also, the loss depends on the type of intelligence measured. *Crystallized intelligence*—skills and overlearned knowledge—remains stable or improves; vocabulary and general knowledge, for example, improve through the seventh decade of life (Harada, Love, & Triebel, 2013).

Fluid intelligence, which includes problem solving, reasoning, and the ability to process and learn new information, declines beyond the third decade. A major component of fluid intelligence is processing speed, which includes the speed of performing cognitive activities and the speed of motor responses. Processing speed begins to decline in the third decade (Harada et al., 2013). Schaie (1994) found that statistically removing the effects of speed from test scores significantly reduced elderly individuals' performance losses. We saw earlier that working memory is especially important to intellectual capability. In a study of higher-order information processing, speed accounted for 80% of the variance in general intelligence, leading the researchers to suggest that general intelligence is little more than this capability (Schubert, Hagermann, & Frischkom, 2017).

You know that a determinant of general intelligence is the ability to integrate activity between brain areas. Even in healthy aging there is a loss of coordination in the **default mode network**, portions of the frontal, parietal, and temporal lobes that are active when the brain is at rest or focused internally rather than on the outside world; activity in the default mode network is thought to represent preparedness for action. As white matter connections decline, so does this coordination, along with cognitive ability (Andrews-Hanna et al., 2007; Broyd et al., 2009). Elderly individuals with better whole-brain network efficiency (clustering and short path length) had higher processing speed and superior executive functions, including impulse control and decision making (Berlot, Metzler-Baddeley, Ikram, Jones, & O'Sullivan, 2016; Wen et al., 2011).

The brain does have ways of compensating, such as the increased metabolism that is seen in subjects with mild intellectual disability and the recruitment of frontal areas in people with dyslexia during reading (see Chapter 9). Studies of elderly individuals who are "aging gracefully" indicate that they are holding their own through additional neural effort (Helmuth, 2002). For example, older adults had to activate both prefrontal areas to perform a memory task as well as young adults, who activated

only the right prefrontal cortex (Figure 13.13; Cabeza, Anderson, Locantore, & McIntosh, 2002). The increase in frontal activity was in proportion to decreases in other areas, which supports the idea that the shift serves a compensatory function (S. W. Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008). Compensation may not be limited to frontal activity; it has also been observed in the parahippocampal area during a memory recognition task (van der Veen, Nijhuis, Tisserand, Backes, & Jolles, 2006). Another way elderly individuals can compensate is by practicing skills. Elderly individuals who initially coped with a task via compensation showed brain patterns like those of young subjects after just 5 hours of training on the task (Erickson et al., 2007).



Description

Figure 13.13 Compensatory Brain Activity in High-Performing Older Adults.
A memory task activated the right prefrontal area in young and in low-performing older adults. Older adults who performed as well as the young showed activation in both prefrontal areas.

Source: From "Aging Gracefully: Compensatory Brain Activity in High-Performing Older Adults," by R. Cabeza et al., *NeuroImage, 17*, pp. 1394–1402, fig. 2, p. 1399. © 2002 Elsevier.

Some of the loss in performance is due to lack of opportunity to use skills. In one study, aged individuals regained part of their lost ability through skills practice, and many of them returned to their pre-decline levels; they still had some advantage over controls 7 years later (Schaie, 1994). Elderly people also improved in memory test scores when their self-esteem was bolstered by presenting them with words that depict old age in positive terms, such as *wise*, *learned*, and *insightful* (B. Levy, 1996).

Loss in performance that has a physical basis may be reduced if not reversed. Diet appears to be one factor; age-related decline can be reduced by consuming fish more than once per week (B. Qin et al., 2014) and by having a cup of tea every day, even in individuals with the *ApoE* allele (Feng et al., 2016). Both of these foods have anti-inflammatory and antioxidant effects. Vitamin supplements might also help. In elderly individuals with mild cognitive impairment, a combination of B vitamins reduced the rate of brain atrophy 50% and slowed cognitive decline, compared with controls given a placebo (C. A. de Jager, Oulhaj, Jacoby, Refsum, & Smith, 2012; Douaud et al., 2013). The B vitamins slow gray matter atrophy by reducing homocysteine, a toxic compound that is elevated in people with a diet high in animal proteins.

Estrogen also provides some protection against the cognitive effects of aging. In a 13-year study of elderly women, both endogenous estrogen levels and estrogen replacement therapy were associated with higher cognitive performance (Matyi, Rattinger, Schwartz, Buhusi, & Tschanz, 2019). How does estrogen improve cognitive performance? From studies of hormonal fluctuation during the menstrual cycle, we know that higher estrogen levels are correlated with cortical excitability (M. J. Smith et al., 1999), increased glucose metabolism (Reiman, Armstrong, Matt, & Mattox, 1996), blood flow in areas involved in cognitive tasks (Dietrich et al., 2001), and responsiveness to acetylcholine, which is important in memory and cognitive functioning (O'Keane & Dinan, 1992). In older, menopausal women, those who receive estrogen replacement do better on tests of working memory, response switching, and attention (Keenan, Ezzat, Ginsburg, & Moore, 2001).

So what about the male of the species? Men who maintain testosterone production past the age of 50 have better preserved visual and verbal memory and visual-spatial functioning (Moffat et al., 2002). The effects of replacement therapy have been variable, owing apparently to the form of the testosterone preparation used. However, numerous studies have shown improvement in spatial, verbal, and working memory (Cherrier, Craft, & Matsumoto, 2003; Cherrier et al., 2005; Gruenewald & Matsumoto, 2003). Interestingly, testosterone improves only spatial memory; additional memory improvement requires that the testosterone be delivered in the form of dihydrotestosterone, which can be converted to estrogen in the brain by the process of aromatization (Cherrier et al., 2003, 2005). When it comes to cognitive abilities, we could be tempted to consider estrogen a wonder drug.

So losses are smaller than believed, and they differ across people and across skills. In addition, continued use of skills, esteem enhancement, and hormone therapy may slow cognitive decline during aging. Obviously, we should not stereotype the older individual as a person with diminished abilities.

Intellectual Disability

Intellectual impairment was previously referred to as retardation, but that term has taken on such negative meaning in popular usage that practitioners and authorities

are shifting to the term *intellectual disability*. **Intellectual disability (ID)** is a limitation in intellectual functioning (reasoning, learning, problem solving) and adaptive behavior that is developmental in origin. The criteria set by the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM*-5), are an IQ at or below 70; deficits in adaptive functioning, such as communication, social participation, and independent living; and onset during the developmental period (American Psychiatric Association, 2013). Looking back at Figure 13.2, you can see that 2% of the population falls in this IQ range, and a lower percentage would meet the additional two criteria. Table 13.1 describes the areas of impairment that contribute to a diagnosis of functional impairment. Any definition is not only arbitrary but situational and cultural as well; a person considered to have an intellectual disability in our society might fare reasonably well in a simpler environment. The situational nature is illustrated by the fact that many individuals shed the label as they move from a childhood of academic failure into adulthood and demonstrate their ability to live independent lives.

Table 13.1

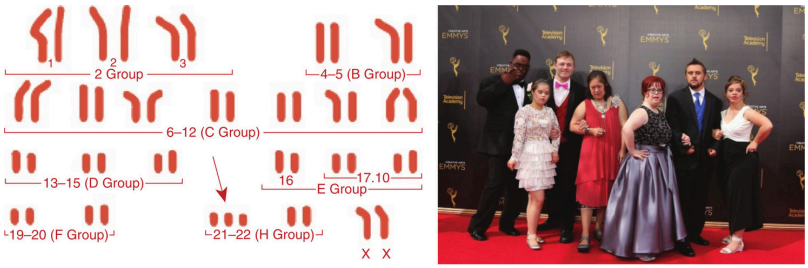
TABLE 13.1 Areas of Impairment Leading to a Diagnosis of Intellectual Disability.

DOMAIN	INCLUDES . . .
Conceptual	Skills in language, reading, writing, math, reasoning, knowledge, and memory
Social	Empathy, social judgment, interpersonal communication skills, ability to make and retain friendships
Practical	Self-management in areas such as personal care, job responsibilities, money management, recreation, and organizing school and work tasks

Intellectual disability has an estimated prevalence of just over 1% worldwide, with a higher incidence in low- and middle-income countries (Maulik, Mascarenhas, Mathers, Dua, & Saxena, 2011). It can result from childhood infections, birth complications, extreme malnutrition, and, as you saw in Chapter 5, maternal alcohol abuse during pregnancy. Although intelligence is highly heritable, no reliable estimates of the heritability of ID exist. Determining which genes are at fault has also been difficult, in part because ID is made up of a large number of disorders. Another problem is that while milder forms of ID involve common forms of inheritance, severe ID more often results from *de novo* mutations, those that appear spontaneously in the individual rather than being passed down from the parents (Vissers, Gilissen, & Veltman, 2016). Nevertheless, more than 700 genes have been convincingly linked to ID; however, this very fact means that we can expect additional genes to have small effects and to be difficult to isolate.

The most common genetic cause of ID is Down syndrome, with a prevalence of 1 in every 700 births (S. E. Parker et al., 2010). Usually caused by the presence of an extra 21st chromosome (trisomy 21), **Down syndrome** typically results in individuals with IQs in the 40 to 55 range, although some are less impaired (Figure 13.14). Recall that the amyloid precursor protein gene that is involved in early-onset Alzheimer's disease is located on chromosome 21 and that it was discovered because Down syndrome individuals also develop amyloid plaques (Goate et al., 1991; Murrell, Farlow, Ghetti, & Benson, 1991). Ninety-five percent of people with Down syndrome have the entire extra chromosome; a smaller number have the extra chromosome only in some of the body's cells, and a few have only an end portion of the chromosome, which is attached to another chromosome. Mouse models of Down syndrome have been very useful in studying the disorder and attempting new treatments. The most frequently used model is the Ts65Dn mouse, engineered with a third copy of 55% of chromosome 21. Ts65Dn mice were treated prenatally and in the early postnatal period with a peptide that supports neural survival and development; this prevented developmental delay and reduced long-term memory impairment in adulthood (Kazim, Blanchard, Bianchi, & Ibal, 2017). However, it may be an oversimplification to focus only on the effects of chromosome 21 genes. DNA methylation differs by more than 10% between individuals with Down syndrome and controls, and the degree of methylation difference is correlated with cognitive function (Dekker, De Deyn, & Rots, 2014). Although the differentially methylated genes were

found on other chromosomes, the authors attributed the hypermethylation to the presence of the third chromosome 21.



Description

Figure 13.14 Down Chromosomes and *Born This Way*.
(a) Chromosomes of a person with Down syndrome (female). The arrow points to the three 21st chromosomes. (b) Some individuals with Down syndrome are more fortunate than others. The documentary series *Born This Way* follows seven young people with Down syndrome in Southern California as they pursue their various careers and dreams.

Sources: (a) © www.nads.org, 2007. (b) Everett Collection Inc/Alamy Stock Photo.

? What causes intellectual disabilities?

Another frequent genetic cause of ID is **fragile X syndrome**, which is due to a mutation in the fragile X mental retardation 1 gene (*FMR1*). The *FMR1* gene normally contains between 6 and 45 repetitions of the nucleotide sequence C, G, G. If the number of CGG repeats reaches 200, the gene is turned off, and no protein is made. Fragile X syndrome is the result, with IQs typically below 75. An intermediate number of CGG repeats results in reduced protein production, accompanied by a slight increase in the chance of ID. Males are affected more often, and when fragile X does occur in females, the symptoms are usually milder. In *FMR1* knockout mice, unusual numbers of dendrites indicate a failure to prune excess synapses during development (A. B. Patel, Loerwald, Huber, & Gibson, 2014).

Phenylketonuria is due to an inherited inability to metabolize the amino acid phenylalanine; the excess phenylalanine interferes with myelination during development. Newborn infants are routinely tested for phenylalanine in the urine or blood, and ID can be prevented by avoiding foods containing phenylalanine. The artificial sweetener aspartame is a familiar example of a substance that is high in phenylalanine. Without dietary treatment, the individual has severe or profound disabilities, with an adult IQ around 20 points.

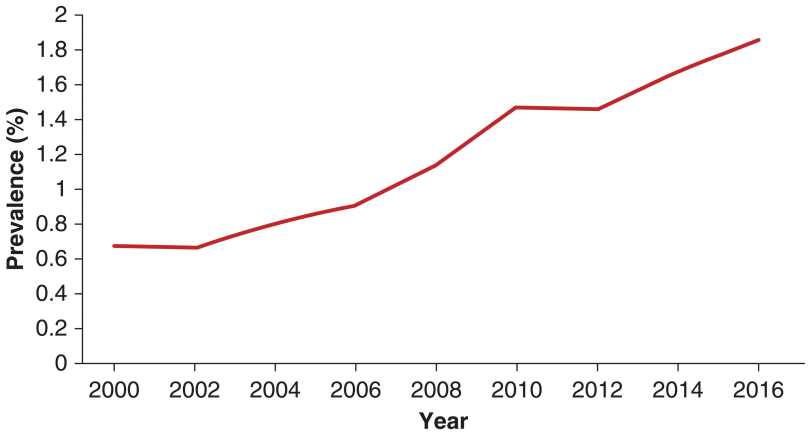
Hydrocephalus occurs when cerebrospinal fluid builds up in the cerebral ventricles; the increased fluid volume crowds out neural tissue, usually causing ID (Figure 13.15). As we saw in Chapter 3, hydrocephalus can also be treated if caught early, by installing a shunt that prevents the accumulation of the excess cerebrospinal fluid. Also in that chapter, you learned that some individuals seem not to be harmed by the dramatic loss of cortex; in fact, half of those whose ventricles fill 95% of the cranium have IQs over 100 (Lewin, 1980).

Figure 13.15 The Hydrocephalic Brain.
Hydrocephalic brain. Notice the large lateral ventricles and the small amount of cortex around the perimeter in the hydrocephalic brain.

Dr. Najeeb Layyous/Science Source

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a set of neurodevelopmental disorders characterized by social deficits, communication difficulties, and repetitive behaviors. In *DSM*-5, ASD includes the previously used diagnoses of autism, Asperger syndrome, pervasive developmental disorder not otherwise specified, and childhood disintegrative disorder (American Psychiatric Association, 2013). Although the term *autism* refers to a subset of these disorders, it is used interchangeably with *autism spectrum disorder* in the profession; we will follow suit in the following discussion, especially when describing older studies, which used narrower diagnostic criteria. The prevalence of ASD was 1 in 150 children (.67%) in the years 2000 and 2002 but increased to 1 in 68 by 2010 (1.5%) and appeared to level off before rising to 1 in 54 (1.85%) in 2016, the most recent year for which we have data (Figure 13.16; Centers for Disease Control and Prevention, 2020a). Rates in North America, Asia, and Europe are similar, averaging between 1% and 2%. At least some of the increase can be attributed to improved detection, broader diagnostic criteria, and doctors' greater willingness to use the label because of decreasing stigmatization of autism and because the diagnosis will qualify the family for increased services and financial assistance (Rutter, 2005). Some observers believe the increase is real and due, for example, to rising environmental toxins, but the position of most authorities is that we simply don't know how much the actual rate has increased or why. One statistic is not in dispute: The prevalence is more than four times higher among boys than girls (Centers for Disease Control and Prevention, 2020b).



Description

Figure 13.16 Prevalence of Autism Spectrum Disorder, 2000–2016.

Source: Based on data from "Data & Statistics on Autism Spectrum Disorder," by Centers for Disease Control and Prevention, 2020.

Cognitive and Social Impairment

One third of children with ASD have ID, defined as IQ < 70; this percentage is higher in girls than boys (40% versus 32%) and among black and Hispanic compared to white children (47%, 36%, and 27%, respectively; Centers for Disease Control and Prevention, 2020b). Individuals with autism share a common core of impairment in communication, imagination, and socialization (Frith, 1993). Trouble understanding verbal and nonverbal communication often makes testing difficult, raising questions about the meaningfulness of test results. In some cases, nonverbal tests such as the Raven Progressive Matrices are used, or IQ is estimated from an assessment of adaptive behavior, but these do not eliminate the deficits. Difficulty with imagination also is common, in the form of an inability to pretend or to understand make-believe situations. Use of language is also very literal—"Can you pass me the salt?" is met with "Yes" with no compliance—and in some cases, this literalism extends to an obsessive interest in facts, like that seen in the movie *Rain Man*.

? What is autism like?

These characteristics make it difficult to socialize with others, which is what sets apart children with autism the most. They usually prefer to be alone, and they ignore people around them when they can't (Figure 13.17). Their interaction with others often is limited to requests for things they want; they otherwise treat people as objects, sometimes even walking or climbing over them. Verbalization is usually limited, and the child often repeats what others say (echolalia).

Figure 13.17 Individuals With Autism Typically Feel Threatened by Social Interaction. A typical symptom in children with autism is the need for order in their world, often expressed by meticulously lining up their toys.

Source: iStock/UrsaHoogle.

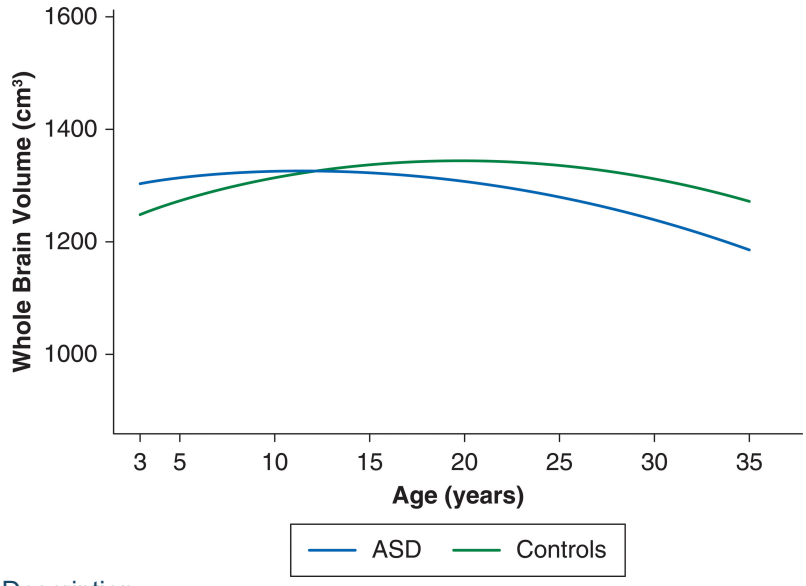
Some researchers believe that much of the social behavior problem is that the person with autism lacks a **theory of mind**, the ability to attribute mental states to oneself and to others. In other words, the person with autism cannot infer what other people are thinking. One man with autism said that people seem to have a special sense that allows them to read other people's thoughts (Rutter, 1983), and an observant youth asked, "People talk to each other with their eyes. What is it that they are saying?" (Frith, 1993). In a study that measured this deficiency, children watched hand puppet Anne remove a marble from a basket where puppet Sally had placed it and put it in a box while Sally was out of the room. On Sally's return, children were asked where she would look for the marble. Normal 4-year-olds had no problem with this task, nor did Down syndrome children with a mental age of 5 or 6. But 80% of children with autism with an average mental age of 9 answered that Sally would look in the box (Frith, Morton, & Leslie, 1991).

There are two hypotheses as to how we develop a theory of mind. According to the "theory theory," we build hypotheses over time based on our experience. Simulation theory holds that we gain insight into people's thoughts and intentions by mentally mimicking the behavior of others. This view gets some support from studies of the mirror neurons we talked about in Chapters 8 and 9. Individuals who score higher on a measure of empathy tend to have more activity in these mirror neurons (Gazzola, Aziz-Zadeh, & Keysers, 2006). Researchers have suggested that impaired mirror functions reduce the ability of a person with autism to empathize and to learn language through imitation. Children with ASD engage in less contagious yawning than other children do (Senju et al., 2007), and they show neural deficiencies during mirroring tasks. For example, they can imitate others' facial expressions, but mirror neuron activity while doing so is either delayed or nonexistent (Dapretto et al., 2005; Oberman, Winkielman, & Ramachandran, 2007). Other studies show reduced activation in the inferior frontal cortex and motor cortex, suggesting weakness in the dorsal stream connections that provide input to those areas (Nishitani, Avikainen, & Hari, 2004; Villalobos, Mizuno, Dahl, Kemmotsu, & Müller, 2005). This interpretation was supported in a study of individuals diagnosed with Asperger syndrome, the former term for high-functioning autism. When they imitated facial expressions, transmission over the dorsal stream (occipital to superior temporal to posterior parietal to frontal) was delayed by 45 to 60 milliseconds compared with normal controls (Nishitani et al., 2004).

Brain Anomalies in Autism

Autism was long thought to be purely psychological in origin, because no specific brain defects had been found. The problem was blamed on a lack of maternal bonding or a disastrous experience of rejection that caused the child to retreat into a world of aloneness (Frith, 1993). But no evidence could be found for this kind of influence; children with autism often had exemplary homes, and children with extremely negative experiences did not develop autism. The frequent association with ID and epilepsy implied that autism was a brain disorder.

There are many anomalies in the brains of individuals with autism, but the most striking characteristic is the atypical sequencing of brain development. The strongest data come from a study in which participants received multiple scans between the ages of 3 and 35 to provide a semblance of longitudinal data (N. Lange et al., 2015). As you can see in Figure 13.18, brain volume is greater in children with ASD when the study begins at the age of 3. The overgrowth starts to level off around the age of 5 or 6 and is followed by a decline. Between the ages of 10 and 15, the children with ASD begin to fall below the controls, and this decline continues throughout the study. Notice that the two lines in the graph follow similar patterns, differing only in timing and degree. This suggests that the brain volume changes in ASD are exaggerations of the synaptic growth and later pruning that are seen in normal brain development (Gilbert & Man, 2017).



Description

Figure 13.18 Changes in Whole-Brain Volume in Patients With ASD and Controls. By the age of 3, the brains of children with ASD are significantly larger than those of unaffected children. Between the ages of 10 and 15, their brain volumes decrease below that of the controls and continue to decrease until the brains are much smaller at age 35.

Source: Adapted from Figure 2 of N. Lange et al., 2015.

Not every child with ASD develops an enlarged brain; some have normal-sized brains, and about 20% are born with an abnormally small head and brain (microcephaly). Microcephaly is associated with the severest symptoms, including ID (Gilbert & Man, 2017). This illustrates the fact that ASD is very heterogeneous physiologically, affecting the brain differently and in different locations in different individuals. The variability between individuals in physiology and symptoms has led some researchers to speak of “the autisms,” as if it consists of multiple disorders. There has been some progress in distinguishing subgroups based on their genetic profiles, but the most obvious subgrouping is gender based. Unfortunately, ASD is

less understood in females, partly because there are so few of them and studies of males outnumber those of females 23 to 1. The behavioral manifestations tend to be different; while males are more likely to engage in externalizing behaviors (aggression, hyperactivity, and repetitive behavior), females more often internalize their symptoms in the form of anxiety and depression. The threshold for developing ASD is elevated in females, perhaps due to protective effects of estrogens during brain development as well as to having two Y chromosomes. Females with ASD have a greater load of ASD-related genes, greater differences in white and gray matter, and greater enlargement of the amygdala. The mechanisms that lead to the development of ASD might differ between males and females, or some undetermined female protective factors could prevent females from succumbing until the genetic and neural assaults are extreme.

Several studies have reported reductions in white matter integrity and structural connectivity in the brains of individuals with ASD, particularly in the corpus callosum and other long-distance connections (Aoki et al., 2017; Dimond et al., 2019; Wilkinson, Wang, van der Kouwe, & Takahashi, 2016). In a study of high-risk infants, those who developed ASD by 24 months already had reduced white matter integrity at the age of 6 months (Wolff et al., 2012). These findings have led to the hypothesis that underconnectivity is a fundamental characteristic of the disorder, but hyperconnectivity of some connections is also seen in the same brains (Iidaka, Kogata, Mano, & Komeda, 2019; Linke, Keehn, Pueschel, Fishman, & Müller, 2018). We're accustomed to thinking of greater connectivity as an asset, but hyperconnectivity represents an excess, and it is correlated with more severe ASD symptoms. Hypoconnectivity particularly disrupts connections within the cortex, including interhemispheric connections across the corpus callosum; hyperconnectivity is less extensive and mostly confined to subcortical regions (Figure 13.19; Di Martino et al., 2014).

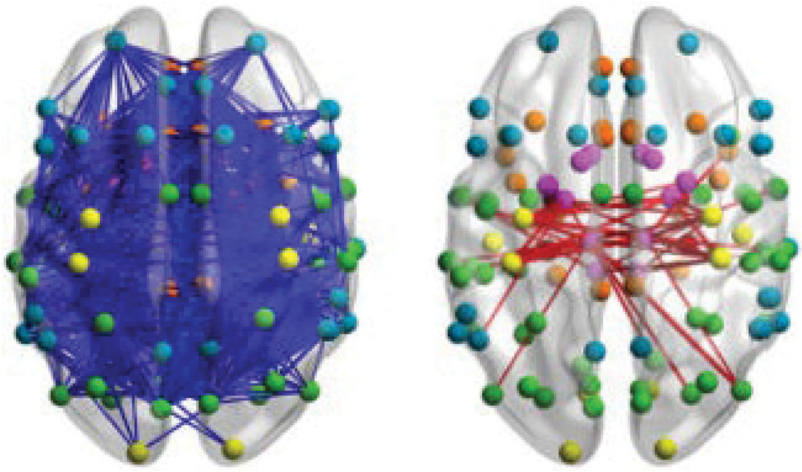


Figure 13.19 Hypoconnectivity and Hyperconnectivity in the Brains of Males With ASD.
Blue lines represent connections that were significantly weaker in ASD versus controls (left); red lines represent connections that were significantly stronger in ASD versus controls (right). (The colors of the circles indicate types of connections.)

Source: From Figure 2 of "The Autism Brain Imaging Data Exchange: Towards Large-Scale Evaluation of the Intrinsic Brain Architecture in Autism," by A. Di Martino et al. (2014), *Molecular Psychiatry*, 19, 659–667.

However, some children with ASD who had stronger connections between the thalamus and the auditory cortex had fewer deficits in language, communication, and social cognition, as well as fewer repetitive behaviors (Linke et al., 2018; Nair et al., 2015). This happened only in the subgroup with reduced connectivity between the left and right auditory areas, which in all the other children led to poorer auditory processing and lowered verbal IQ. Apparently developing stronger thalamic-auditory

cortex connections compensated for the loss of ability to share information between the auditory areas and rescued a portion of normal behavior.

Biochemical Anomalies in Autism

One of the most popular ideas about the origins of ASD is that it arises from a hyper-excitable brain; the behavioral manifestations include inattention, excitability, and seizures. There is evidence this overactivity may derive from an excitation/inhibition imbalance due to excessive glutamate activity or a deficit of GABA (gamma-aminobutyric acid) activity; you may remember these as the brain's primary excitatory and inhibitory transmitters, respectively (Deweerdt, 2019; Marotta et al., 2020). There is little evidence that GABA modulators treat the core symptoms, but therapeutic results have been reported for drugs that alter functioning of the NMDA glutamate receptor. NMDA receptor antagonists (memantine, amantadine) reduce social and cognitive deficits, inattention, and hyperactivity and other symptoms. On the other hand, an NMDA receptor agonist (D-cycloserine) reduces social withdrawal and repetitive behavior (E.-J. Lee, Choi, & Kim, 2015). Apparently, deviations from normal functioning of the glutamate system in either direction can produce different symptoms of ASD in different individuals.

Serotonin contributes to brain development, including synapse formation and pruning. About one third of people with ASD have elevated blood levels of serotonin, but serotonin synthesis is reduced in a subset of children with autism (Hwang, Mohamed, & Brašić, 2017). Several studies attempted treatment with fenfluramine, an indirect serotonin antagonist, but without success in reducing core symptoms. Treatment with SSRIs, antidepressants that increase serotonin availability at the synapses by blocking reuptake into the terminals, has been ineffective with children and minimally effective with adults (Hwang et al., 2017; Reddihough et al., 2019; K. Williams, Brignell, Randall, Silove, & Hazell, 2013). These failures may have occurred because the subject pools included individuals from both subgroups.

According to the dopamine hypothesis of ASD, deficits in social behavior are due to reduced dopamine activity in the mesocorticolimbic reward system, and stereotyped (repetitive, purposeless) motor behaviors are caused by excess dopamine activity in the nigrostriatal circuit (substantia nigra to dorsal striatum; Pavăl, 2017). Because both of these behaviors are also seen in schizophrenia and other psychoses, doctors have tried using antipsychotic drugs to treat ASD. Two antipsychotics, aripiprazole (brand name Abilify) and risperidone (Risperdal), are the only drugs approved by the Food and Drug Administration to treat symptoms of ASD; they are dopamine antagonists, which work by blocking certain dopamine receptors. They are effective in reducing social withdrawal, repetitive behaviors, and hyperactivity (Hirsch & Pringsheim, 2016; Maneeton et al., 2018). These drugs are suitable for short-term use only, because their side effects include significant weight gain and risk for producing involuntary movements, or *tardive dyskinesia*.

In Chapter 7, we saw that oxytocin facilitates bonding and social recognition; for that reason, it is known as the "sociability molecule." Most studies have found that oxytocin is reduced in individuals with ASD, though not in all (reviewed in Anagnostou et al., 2014, and S. Y. Lee et al., 2015). Studies that administered a single dose of oxytocin have reported improvements in repetitive behaviors, self-injury, empathy, social interaction, and ability to recognize mental or emotional state from photos of the eyes. Four weeks of daily treatment with an oxytocin nasal spray produced improvement at 1 month and 1 year in social avoidance and repetitive behaviors (Bernaerts, Boets, Bosmans, Steyaert, & Alaerts, 2020). An fMRI study indicated that oxytocin improves trust by reducing activity in fear areas in the amygdala and midbrain (Figure 13.20; T. Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008). Others indicated that oxytocin improves deficient brain functioning in the right insula during emotional processing (Aoki et al., 2014) and reduces social symptoms by increasing functional connectivity between frontal areas (Watanabe et al., 2015).

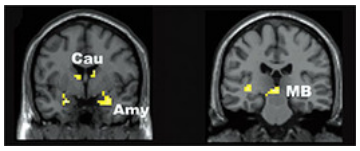


Figure 13.20 Reduced Response to Betrayal of Trust Following Oxytocin. Compared with subjects receiving a placebo, those who received nasally administered oxytocin responded less to betrayal of trust in an investment simulation. Areas of comparatively reduced activity (shown in yellow) were the caudate nucleus (Cau), amygdala (Amy), and midbrain (MB).

Sources: From "Oxytocin Shapes the Neural Circuitry of Trust and Trust Adaptation in Humans," by T. Baumgartner et al., 2008, *Neuron, 58*, pp. 639–650, fig 4.

The Environment and Autism

Parental treatment has been ruled out as the cause of autism, but numerous other environmental conditions have been identified as contributing factors. One's suspicions immediately turn to environmental pollutants, such as those generated by automobile traffic, agricultural practices, and industrial activity. Researchers usually assess such effects by studying people living near agricultural fields or a busy highway, but two studies are notable for employing more meaningful measures of pollution. Using localized estimates of traffic pollution based on EPA data, traffic volume, and climatic conditions during each child's gestational period and first year of life, researchers found that living in homes where traffic pollution was highest was associated with triple the rate of autism (Volk, Lurmann, Penfold, Hertz-Picciotto, & McConnell, 2014). Recognizing that ASD occurs in geographic clusters, University of Chicago researchers used county-level data on genital malformation in male children as a surrogate for environmental exposure and found that the incidence of ASD increased 283% for every percentage point increase in incidence of malformations (Rzhetsky et al., 2014).

There are numerous other environmental risk factors as well (Karimi, Kamali, Mousavi, & Karahmadi, 2017). One is paternal age, possibly due to chromosomal abnormalities that develop with aging. Risk was almost doubled in children of fathers between the ages of 34 and 39 and more than doubled beyond the age of 40. Birth complications can impair later brain development and lead to ASD; cesarean delivery and umbilical cord around the neck increase the risk of autism by 26%. The mother's use of common medications during pregnancy, such as antidepressants or acetaminophen, also raises the risk, as do her health issues, including hypertension and diabetes. Particularly dangerous is maternal infection during the second trimester of pregnancy, which triples the chance of a woman having a child with ASD (Zerbo et al., 2015). The news is not all bad: Mothers who took folic acid during pregnancy were half as likely to bear a child who would later be diagnosed with autism (Surén et al., 2013). And the strongly held belief among some parents that ASD is linked to childhood vaccines doesn't hold up to scientific scrutiny, as A Further Look shows.

A Further Look:

Childhood Vaccines and Autism

Source: From Wakefield et al. (1998)..

In 1998, Andrew Wakefield and several colleagues published a paper in which they linked the measles, mumps, and rubella (MMR) vaccine to autism. Years later, two reviews of all the available studies concluded that there was no credible link between autism and the MMR vaccine or the mercury-derived preservative (thimerosal) used in some vaccines (Demicheli, Jefferson, Rivetti, & Price, 2005; Immunization Safety Review Committee, 2004). In early 2010, the General Medical Council, which oversees doctors in Britain, determined that Wakefield's study was methodologically flawed and that he had acted unethically. *The Lancet*, which published the study, called the report "some of the most terrible behavior in any research" and took the rare action of withdrawing the study (M. Park, 2010). More recently, a comprehensive meta-analysis examined scientific data from more than 1.25 million children and concluded that there was no relationship between vaccines, components of vaccines, or multiple vaccine administrations and the development of autism or ASD (L. E. Taylor, Swerdfeger, & Eslick, 2014).

Many parents whose children's first signs of autism coincided with a round of childhood vaccinations say they find these reports unconvincing. By 2010, more than 5,000 suits had been brought claiming a link between vaccines and autism. This prompted a legal review known as the Omnibus Autism Proceeding, which found no causal link between vaccines and ASD (Hamblin, 2019). In the meantime, there has been a disturbing decrease in the rate of childhood immunization in several countries despite the health risks, leading to large outbreaks of measles and other childhood diseases that could have been prevented. As a result, the World Health Organization has included "refusal to vaccinate" in its top 10 threats to global health (Yan, 2019).

Heredity and Autism Spectrum Disorders

The list of environmental influences is so long it makes one wonder how much is left for genetic influence. It turns out to be a lot. Siblings of children with autism are 25 times more likely to be diagnosed with autism than other children (Abrahams & Geschwind, 2008); the number would be even higher, but parents tend to stop having children after the first autism diagnosis. For the identical twin of a child with autism, the risk of autism is at least 60%; when autistic-like symptoms are considered in the second twin, the concordance jumps to 92%, compared with 10% for fraternal pairs (A. Bailey et al., 1995). In a study of the 7 million children born in Sweden between 1982 and 2006, heritability was estimated at 83%. The variance that could be attributed to nonshared environmental influence was 17% and for shared environment was 4% (Sandin et al., 2017). A study of 2 million children from five countries agreed, placing the heritability estimate at 81%. Interestingly, the values varied by country, ranging from 51% to 87% (Bai et al., 2019). When we look at epigenetic effects and *de novo* mutations that are not shared with parents and siblings, we realize that genes have additional effects that are not recognized in heritability estimates.

It soon became clear that the genes responsible for ASD were numerous and had very small effects; to make finding them all the more difficult, relatively few afflicted people in a study will share the same genes. Genes that have been identified include those responsible for proteins involved in synapse formation and the neurotransmitters we identified earlier (along with others) and their receptors. The transmitters are important not only for their role in neural communication but also because they contribute to neuronal migration, differentiation, and synapse formation and pruning during development (Marotta et al., 2020; Rylaarsdam & Guemez-Gamboa, 2019).

Researchers have looked to genes for an explanation of the greater male risk for ASD. The search for the obvious candidates, X-linked genes, has not been very fruitful. There is, however, some genetic support for the "female protective model" we mentioned earlier (Jacquemont et al., 2014). Females may gain a benefit from the RORA protein, which regulates the activity of more than 2,500 genes; some of these are involved in neuron and synapse development and synaptic transmission, and at least six have been associated with ASD (Sarachana & Hu, 2013). The *RORA* gene is upregulated by estrogens and downregulated by testosterone, and the protein is higher in females than in males (V. W. Hu, Sarachana, Sherrard, & Kocher, 2015; Sarachana & Hu, 2013).

Irene Voineagu and her colleagues (2011) identified more than 500 genes that were expressed at different levels between the frontal and temporal cortices of healthy brains and only eight in ASD brains. As you have seen before, environmental influences almost certainly exert their effect through epigenetic modification of gene expression; this fact offers a glimmer of hope in that drugs designed to reverse those modifications might be used as a treatment for autism (Siniscalco, Cirillo, Bradstreet, & Antonucci, 2013).

Autistic Savants and High-Functioning Autism

A *savant* is a person with exceptional intellectual skills, beyond the level of "typical" genius, such as Leonardo da Vinci or Albert Einstein. However, the term is more frequently used to describe individuals who have one or more remarkable skills but whose overall functioning is below normal; half of these individuals with islands of exceptional capabilities are **autistic savants** (Treffert & Christensen, 2006). Some can play a tune on the piano after hearing it once, another can memorize whole books, while others take cube roots of large numbers in their heads or calculate the day of the week for any date thousands of years in the past or future. Stephen Wiltshire's remarkable talent is for architectural art; after brief helicopter flights, he has produced a detailed drawing of a 4-square-mile (10-square-kilometer) area of London and a 98-foot-long (30-meter-long) mural of Hong Kong's Victoria Harbor and the surrounding cityscape (see Figure 13.21; Stephen Wiltshire MBE—Biography, n.d.). A few "ordinary" individuals can perform similar feats, but the savant's performance is typically faster, more automatic, and without insight into how it is done (A. W. Snyder & Mitchell, 1999). The savant's exceptional capability may be limited in scope, however; some who are calendar calculators cannot even add or subtract with accuracy (O. Sacks, 1990).

Figure 13.21 Stephen Wiltshire With One of His Drawings.
He completed this drawing after observing the site only briefly.

Source: Dan Kitwood/Staff/Getty Images News/Getty.

The source of the autistic savant's enhanced ability is unknown. Dehaene (1997) suggests that it is due to intensely concentrated practice, but more typically the skill appears without either practice or instruction, as in the case of a 3-year-old girl with autism who began drawing animated and well-proportioned horses in perfect perspective (Selfe, 1977). Allan Snyder and John Mitchell (1999) believe that these capabilities are within us all and are released when brain centers that control executive or integrative functions are compromised. This, they say, gives the savant access to speedy lower levels of processing that are unavailable to us. But lacking the executive functions, the savants perform poorly on apparently similar tasks that require higher-order processing. The idea gains some credibility from the case of a man impaired in his left temporal and frontal areas by dementia; despite limited musical training, he began composing classical music, some of which was performed publicly (B. L. Miller, Boone, Cummings, Read, & Mishkin, 2000; also see Figure 13.22). The best-known savant was Kim Peek, the model used by Dustin Hoffman in his portrayal of Raymond Babbitt in *Rain Man*; Peek's brain had several anomalies, particularly in the left hemisphere (Treffert & Christensen, 2006). A few researchers have attempted to unleash savant-like capabilities by using transcranial electrical or magnetic stimulation to inhibit neural activity in the frontal-temporal area (A. Snyder, 2009). Most of the results have been unremarkable, but 40% of volunteers receiving excitatory right-hemisphere stimulation along with inhibitory left-hemisphere stimulation were able to solve a problem that none of the control subjects could solve (Chi & Snyder, 2012). Whatever the explanation, the phenomenon adds to the argument that intellectual ability involves multiple and somewhat independent modules.

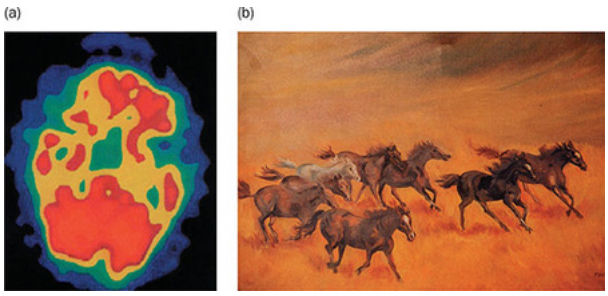


Figure 13.22 Savant-Like Ability Following Brain Impairment.
(a) The scan is from a 64-year-old woman with dementia in the left frontal-temporal area, which shows less activity than the right. (b) After the onset of her dementia, she began to create remarkable paintings like the one here.

Source: From "Emergence of Artistic Talent in Frontal-Temporal Dementia," by B. L. Miller et al., *Neurology, 51*, pp. 978–982. Copyright © 1998. Reprinted by permission of Wolters Kluwer.

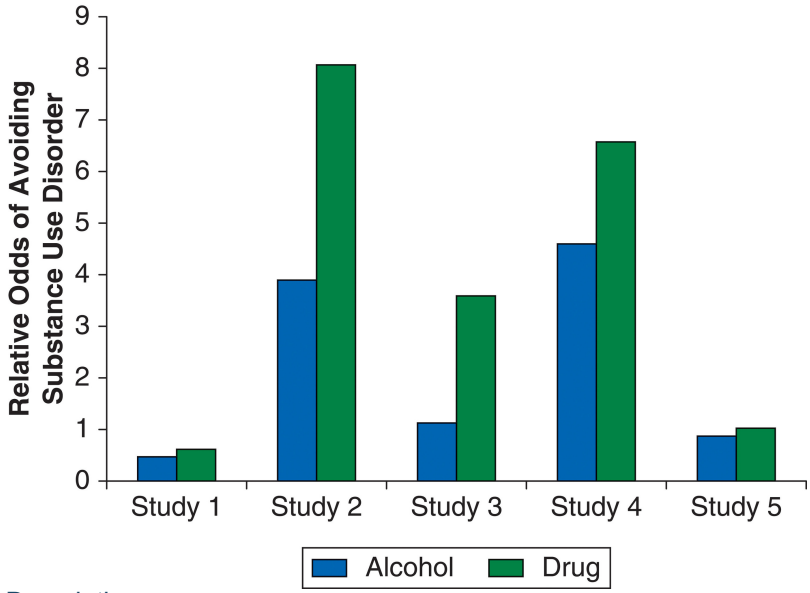
If these savants have an island of exceptional ability, autism is an island of impairment in high-functioning individuals with ASD. As an infant, Temple Grandin would stiffen and attempt to claw her way out of her affectionate mother's arms (O. Sacks, 1995). She was slow to develop language and social skills, and she would spend hours just dribbling sand through her fingers. A speech therapist unlocked her language capability, starting a slow emergence toward a normal life. Even so, she did not develop decent language skills until the age of 6 and did not engage in pretend play until she was 8. As an adult, Grandin earned a doctorate in animal science; she teaches at Colorado State University and designs humane facilities for cattle, while lecturing all over the world on her area of expertise and on autism. Still, her theory of mind is poorly developed, and she must consciously review what she has learned to decide what others would do in a social situation. She says that she is baffled by relationships that are not centered on her work and that she feels like "an anthropologist on Mars."

Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD) is characterized by impulsiveness, inability to sustain attention, learning difficulty, and hyperactivity. Behaviorally, what we see is fidgeting and inability to sit still, difficulty organizing tasks, distractibility, forgetfulness, blurting out answers in class, and risk taking (Smalley, 1997). Diagnosticians recognize three types of ADHD; combined inattention and hyperactivity-impulsiveness is most common, but some individuals are predominantly inattentive or predominantly hyperactive-impulsive. ADHD is the most common among childhood-onset behavioral disorders. A meta-analysis of 179 studies estimated prevalence at 7.2% worldwide (Thomas, Sanders, Doust, Beller, & Glasziou, 2015); boys are more than twice as likely as girls to be diagnosed (Visser et al., 2014). Although ADHD is often thought of as a learning disorder (and many children with ADHD do have at least one learning disability), its effects are felt in every aspect of a person's life. Besides having the expected difficulties with life and work, these individuals have greatly increased rates of antisocial personality disorder, criminal behavior, and drug abuse (Biederman, 2004); in fact, 35% of people seeking treatment for cocaine abuse have a history of childhood ADHD (F. R. Levin, Evans, & Kleber, 1998). People with ADHD are also twice as likely to die prematurely, mostly from accidents (Dalsgaard, Østergaard, Leckman, Mortensen, & Pedersen, 2015).

Drugs are usually prescribed to control the symptoms of ADHD, and from 2002 to 2010, the prescription rate jumped 46% in the United States (Chai et al., 2012), while in Denmark it went up a whopping 630% (Dalsgaard, Nielsen, & Simonsen, 2013). With 69% of diagnosed children taking medication (Visser et al., 2014), some observers have raised concerns that children are being overdiagnosed and overmedicated as an easy solution to classroom behavioral problems. The link with drug abuse fostered concerns that treating children with stimulant drugs such as

methylphenidate (Ritalin) and amphetamine was leading to addiction later in life. However, research that followed children with ADHD into adolescence and adulthood revealed that, at worst, stimulant treatment made no difference (Barkley, Fischer, Smallish, & Fletcher, 2003) and that it might even be protective against drug abuse (Figure 13.23; Wilens, Faraone, Biederman, & Gunawardene, 2003). The more positive outcome for the treated individuals could have been due to the reduction of symptoms, or it could have been the result of other factors, such as the support of parents who opted for treatment, but at least these results do not support fears that the medications act as gateway drugs.



Description

Figure 13.23 Relative Odds of Avoiding Substance Abuse Disorder in Individuals Receiving Stimulant Treatment for ADHD as Children, Compared With Those Not Receiving Stimulant Treatment.
Individuals with ADHD who were treated with a stimulant drug as children were as much as 4.6 times as likely to be free of alcohol abuse disorder as individuals who did not receive stimulant treatment and up to 8.1 times as likely to be free of a drug abuse disorder. Values below 1 indicate that treated individuals in that study were at greater risk.

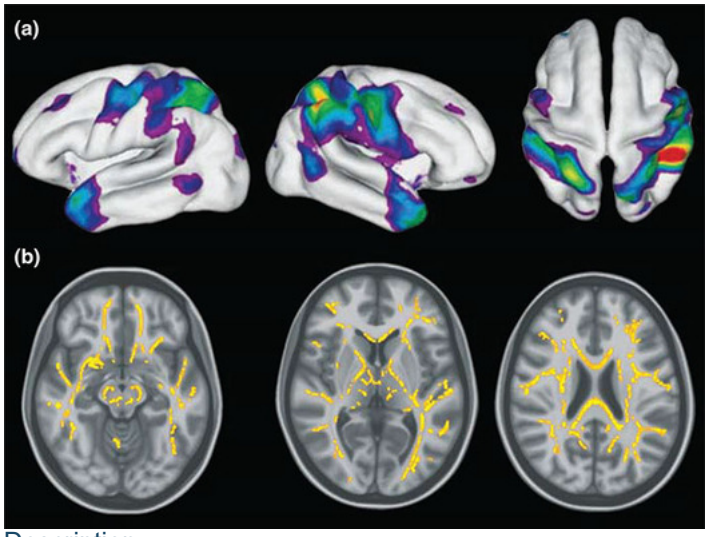
Source: Based on data from Wilens et al. (2003).

Nevertheless, concerns about treating young children with drugs has led to the development of the first medical device to be approved for treating ADHD in children. Used while sleeping, a pocket-sized stimulator delivers pulses of electricity through wires to a small adhesive patch on the child's forehead to stimulate the trigeminal nerve, the cranial nerve that carries sensory information from the face to the brain (J. J. McGough et al., 2019). Research indicated that the stimulation inhibits overactive neurons and stimulates blood flow in areas that control mood, attention, and executive function.

Although ADHD is considered a childhood disorder, a 13-year-long study in the United Kingdom found that 22% of the children with ADHD continued to meet criteria at age 18 (Agnew-Blais et al., 2016). *DSM*-5 diagnostic criteria require onset during childhood, but 68% of the 18-year-olds who met diagnostic criteria without regard to age of onset had not done so in any of the four previous screenings. These results are not unique to the United Kingdom; they were confirmed in a study in Brazil and another in New Zealand (Caye et al., 2016). Unfortunately, the data can't tell us whether adult-onset ADHD is a different form; because the adult-onset group had higher IQs and were predominantly female, the researchers suggested that the individuals might have been able to mask their symptoms during childhood.

Brain Anomalies in ADHD

Numerous studies have reported one difference or another in the brains of individuals with ADHD, but the results have been inconsistent. Brain MRIs cost anywhere between $1,000 and $5,000, so study samples are usually small; brain differences in psychological disorders are typically slight, on the order of just a few cubic centimeters of volume, so reliable detection of these differences requires large samples. Now a nine-country international group has solved that problem by compiling data from 1,700 people diagnosed with ADHD and 1,500 people without (Hoogman et al., 2017). They found reductions in overall brain volume and in five specific structures involved in emotion, motivation, and reward processing: the caudate nucleus, putamen, nucleus accumbens, amygdala, and hippocampus. The amygdala had the most pronounced deficit, which is important because the amygdala has functions not only in emotion but also in response inhibition. Other research has found deficiencies persisting at 33-year follow-up. These included cortical thinning and gray matter reduction in the prefrontal cortex and in parietal-temporal areas concerned with attention (Figure 13.24a; Proal et al., 2011).



Description

Figure 13.24 Cortical Thinning and White Matter Reduction in the ADHD Brain. (a) Areas where the cortex is thinner in individuals with ADHD than in controls. Transitions from purple to red indicate greater thinning. (b) Red and yellow colors indicate where white matter is significantly reduced in the brains of individuals with ADHD, compared with controls.

Source: "Cortical Abnormalities in Children and Adolescents With Attention-Deficit Hyperactivity Disorder," by E. R. Sowell et al., Lancet, 362, figs. 2 & 3, pp. 1702–1703. © 2003 Elsevier Ltd.

White matter integrity also is reduced in children with ADHD, both in interhemispheric connections and in anterior-posterior pathways (Figure 13.24b; Ameis et al., 2016). They share this characteristic with children diagnosed with ASD and obsessive-compulsive disorder. The children with greater white matter impairment also had more impairment in functioning, regardless of their diagnosis. Because of this reduced connectivity, neural activity is localized rather than being integrated across larger areas (Griffiths et al., 2016). The amygdala is the center of a hub of local connections; the researchers suggested that the ADHD brain may be configured to respond impulsively instead of having the neural organization to regulate and inhibit responses.

Genes, Neurotransmitters, and ADHD

To say that ADHD runs in families would be an understatement: Heritability averages 76% across studies (Biederman & Faraone, 2005; Brikell, Kuja-Halkola, & Larsson, 2015), and concordances have been variously estimated at 58% to 83% for identical twins and 31% to 47% for fraternal twins (Wender, Wolf, & Wasserstein, 2001). Like autism, ADHD is a complex, multi-symptom disorder, and different individuals display different combinations of symptoms. Whole-genome studies have implicated genes involved in cell migration, synaptic excitability, and neuronal plasticity (Jain et al., 2012). Another study found 222 copy number variations (CNVs) in ADHD patients that were not found in control subjects (Elia et al., 2010). These CNVs were in or near genes involved in synaptic transmission, neural development, and learning and other psychological functions. Numerous CNVs are in chromosomal locations that have also been identified in autism and schizophrenia (N. M. Williams et al., 2010); participation of a gene in more than one disorder should not be surprising, because different disorders share some symptoms. And remember that we are talking not about a gene for autism or a gene for ADHD or a gene for schizophrenia but about genes that regulate brain growth, receptor development, and so on.

However, the genes most frequently implicated in ADHD are involved with neurotransmission. In fact, it is difficult to discuss the genetics of ADHD without simultaneously discussing neurotransmitters. A review of genetic studies identified 24 “hot genes,” each of which had been linked to ADHD in at least five studies (Z. Li, Chang, Zhang, Gao, & Wang, 2014). The large majority of these genes are involved with dopamine, serotonin, and norepinephrine transmission, including synthesis, transport, and receptors. In addition, one gene’s protein contributes to the construction of the nicotinic acetylcholine receptor. The most frequently prescribed drugs, methylphenidate and amphetamines, increase dopamine and norepinephrine activity by blocking reuptake at the synapse. This implicates both transmitters, but most research links ADHD to reduced activity in dopamine pathways, especially in the prefrontal cortex (Ernst, Zametkin, Matochik, Jons, & Cohen, 1998) and the striatum (K.-H. Krause, Dresel, Krause, Kung, & Tatsch, 2000). These structures’ functions include executive control, impulse inhibition, working memory, movement, learning, and reward—all functions that are affected in ADHD. The significance of reward may be less immediately obvious, but several researchers believe that impaired reward contributes to impulsiveness because the allure of later rewards is too weak to overcome the temptation of immediate gratification (Castellanos & Tannock, 2002; Tripp & Wickens, 2009). Some 20% to 30% of patients do not respond to the traditional medications or cannot tolerate them (Biederman & Faraone, 2005). Two drugs sometimes used in their place, modafinil and atomoxetine, block norepinephrine reuptake, adding support for its role in ADHD as suggested by genetic studies.

The Environment and ADHD

Known environmental contributors to the risk for ADHD include brain injury, stroke, and complications during pregnancy and birth (Biederman & Faraone, 2005; Castellanos & Tannock, 2002). Toxins such as lead are also a factor; although eliminating lead in gasoline and paint has reduced levels in the environment, it is occasionally found in children’s costume jewelry and imported candies, as well as in the soil and water. A recent study confirmed higher blood levels of lead in children diagnosed with ADHD, and lead levels were correlated with teacher and parent ratings of symptoms (Nigg, Nikolas, Knottnerus, Cavanagh, & Friderici, 2010). Since the contamination of the Flint, Michigan, water supply with lead, the number of schoolchildren qualifying for special education services for ADHD, dyslexia, and mild intellectual impairment has increased from 15% to 28% (Green, 2019).

As with autism, another culprit is organophosphate pesticides; children with above-average urinary levels of a metabolite of these pesticides are twice as likely to be diagnosed with ADHD, compared with children with undetectable levels (M. F. Bouchard, Bellinger, Wright, & Weisskopf, 2010). One organophosphate may be especially potent; the risk of ADHD increased—by as much as three times—with increasing urinary levels of dimethylphosphate (C. J. Yu et al., 2016). Other pesticides are also suspect; for example, pyrethroid levels in mothers at gestational

week 28 were associated with ADHD traits in their 2- to-4-year-old children (Dalsager et al., 2019).

The maternal environment is also implicated. ADHD is correlated, for example, with maternal smoking and stress during pregnancy (S. M. Engel et al., 2018; A. Rodriguez & Bohlin, 2005). Even the mother's use of cosmetics, perfumes, and shampoo containing phthalates is turning out to be a problem; mothers who had higher levels of phthalate metabolites in their urine during the second trimester of pregnancy were more likely to have a child diagnosed with ADHD; the rate tripled in mothers in the top 20% of phthalate exposure (S. M. Engel et al., 2018). There is some preliminary evidence that phthalates decrease neurogenesis and proliferation.

It is important to remember that environmental insults often exert their influence by changing gene functioning. For example, inducing concussion in rats altered more than 1,200 genes, 16 of which are linked to ADHD (Q. Meng et al., 2017). Another example is dietary: High fat and sugar in women's diets during pregnancy was associated with higher symptoms of ADHD and with increased methylation of the *IGF2* gene, which is involved in development of brain areas implicated in ADHD (Rijlaarsdam et al., 2017). In addition, genes can influence whether an environmental condition has an effect; in children with ADHD who had a specific mutation in the *C282Y* gene, "safe" levels of lead exposure were associated with increased symptoms (Nigg, Elmore, Natarajan, Friderici, & Nikolas, 2016).

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- Make a list of the kinds of intellectual disability described and their causes.
- What neural and biochemical differences have been found in the brains of people with ASD?
- Why are males more prone to ASD than females?
- Which neurotransmitters are involved in ASD? ADHD?

IN PERSPECTIVE

As important as the assessment of intelligence is in our society for determining placement in school, opportunities for continued education, and employability and promotability, it is remarkable that so much disagreement remains about what intelligence is. This lack of agreement makes it more difficult to study the brain functions that make up intelligence. Nevertheless, we have identified several features that appear to contribute to greater mental power; brain size, neural conduction speed, processing efficiency, and working memory are among these. Although it would be an error to over-localize any function in the brain, we also know that some areas have a special role in important cognitive functions related to intelligence. It remains to be seen whether any characteristic of these areas, such as size, explains why some people have a particularly strong talent in one area, such as creative writing or mathematics. Some people hope that we will eventually have objective brain measures that will tell us exactly how intelligent a person is or whether a child has ASD.

When we reach that point, perhaps another dream will be realized: the ability to diminish or even reverse some of the defects that rob individuals with intellectual disabilities, people with autism, and aged individuals of their capabilities. We may even be able to increase the intelligence of normal individuals. We can only hope that our capacity to make the ethical decisions required keeps pace with our ability to manipulate the human condition.

Chapter Summary

The Nature of Intelligence

- Intelligence is usually assessed with tests designed to measure academic ability.
- Some people show strong abilities not tapped by these tests; our understanding of intelligence should be broader than what tests measure.
- Intelligence theorists are divided over their emphasis on a general factor or multiple components of intelligence.

The Biological Origins of Intelligence

- Probable contributors to general intelligence are brain size, neural conduction speed, processing speed, quality of neural connections, and processing efficiency.
- The involvement of different brain areas suggests multiple components of intelligence.
- About half of the variation in intelligence among people is due to heredity. The closer the family relationship, the more correlated the IQs are. Apparently, many genes are involved; there are several leads to specific genes but little certainty.
- Research has not supported a genetic basis for ethnic differences in intelligence. Adoption has resulted in dramatic increases in IQ above the ethnic group mean.
- Demonstrating which environmental conditions are important has been difficult. Judging by experience with Head Start and similar programs, any influence must be early and intense. Adoption can have dramatic effects if the difference in environments is large.

Deficiencies and Disorders of Intelligence

- Loss of intellectual functioning with age is less than previously believed, and like decreases in learning ability, it is not inevitable. Diminished speed of processing appears to be most important.
- Intellectual disability has many causes, including disease, fetal alcohol syndrome, Down syndrome, fragile X syndrome, phenylketonuria, and hydrocephalus.
- Down syndrome, caused by a partial or full third 21st chromosome, produces mild to moderate intellectual disability.
- Intellectual disability due to phenylketonuria, the inability to metabolize phenylalanine, is severe to profound.
- Hydrocephalus can usually be treated to avoid serious impairment, but some individuals have no apparent deficiencies.
- ASD is partially hereditary, with several gene locations implicated; heritability is around 83%, and the environmental contribution consists mostly of pollution and

maternal factors during gestation.

- ASD involves abnormalities in several brain areas and weak connections among them.
- ASD may involve anomalies in serotonin, glutamate, GABA, and oxytocin functioning.
- Pollutants, paternal age, maternal infection, and other gestational factors can increase the chances of ASD.
- ADHD is a partially genetic disorder characterized by hyperactivity, impulsiveness, and impaired attention and learning; heritability averages 76%. ADHD is associated with a variety of anomalies in functioning and in dopamine, serotonin, norepinephrine, and acetylcholine transmission. Several gene locations have been implicated.
- A variety of environmental influences have been associated with ADHD, including brain injury, toxins, pesticides, and gestational factors.

Study Resources

For Further Thought

- Environmental influences on intelligence have been hard to identify. Does this mean that we are stuck with our genetic destiny?
- Intelligence is subject to physical disorders and genetic and environmental deviations. Speculate about why intelligence is so vulnerable.
- As you look at autism and ADHD, you see several similarities in the causes. Why, for example, do you think one child exposed to organophosphate pesticides would develop ASD and another might be diagnosed with ADHD?

Test Your Understanding

1. Describe the uncertainties about the measurement of intelligence and how this affects the search for biological bases of intelligence.
2. Discuss the brain characteristics that appear to contribute to general intelligence.
3. Discuss what we know about brain and biochemical differences in individuals with autism.

Select the best answer:

1. A problem with most intelligence tests is that they
    1. are not based on theory.
    2. are each based on a different theory.
    3. assess a limited group of abilities.
    4. try to cover too many abilities in one test.
2. Lumpers and splitters disagree on the significance of _____ in intelligence.

    a. heredity

    b. environment

    c. the g factor

d. early education

3. It is likely that _____ is/are important to general intelligence.
    1. the size of neurons
    2. processing speed
    3. processing efficiency
    4. a, b, and c
    5. b and c
4. Research with adults, children, chimpanzees, and monkeys suggests that we are born with
    1. a mechanism for number or quantity.
    2. the ability to do the same things as savants.
    3. many times more intellectual capacity than we use.
    4. time-limited abilities that inevitably deteriorate with age.
5. Research suggests that, normally, environmental effects on intelligence
    1. are almost nonexistent.
    2. are significant but difficult to identify.
    3. are less important than the effect of heredity.
    4. are more important than the effect of heredity.
6. Some observers claim the high correlation between identical twins' IQs occurs because they evoke similar treatment from people. This was refuted by a study in which the correlation
    1. held up when the twins were reared separately.
    2. was unaffected by parents' misidentification of twins as fraternal or identical.
    3. was just as high in mixed-sex as in same-sex identical pairs.
    4. increased as the twins grew older, though they lived apart.
7. The Network Neuroscience Theory claims that intelligence depends on the brain's
    1. white matter integrity.
    2. white matter efficiency.
    3. ability to form new networks.
    4. ability to reconfigure networks.
8. The best evidence that ethnic differences in intelligence are not genetic is that
    1. the various groups perform the same on culture-free tests.
    2. no well-done research has shown an IQ difference.
    3. no genes for an ethnic difference in intelligence have been found.
    4. adoption into a more stimulating environment reduces the difference.
9. Apparently, the most critical effect on intelligence during aging is loss of
    1. speed.
    2. motivation.
    3. neurons.
    4. synapses.
10. Sam has dramatically reduced brain tissue and enlarged ventricles, but his IQ is 105; his disorder is most likely
    1. hydrocephalus.
    2. phenylketonuria.
    3. Down syndrome.
    4. autism.
11. Most mild intellectual disability is believed to be caused by
    1. an impoverished environment.
    2. brain damage sustained during birth.
    3. a combination of a large number of genes.
    4. a combination of environmental and hereditary causes.
12. Research with autism spectrum disorders suggests that autism involves
    1. a single gene.
    2. several genes.
    3. heredity alone.
    4. primarily environment.
13. Impaired sociability in individuals with autism may involve low levels of
    1. risperidone.
    2. serotonin.
    3. thalidomide.
    4. oxytocin.
14. ADHD is associated with reduced or impaired
    1. intelligence.

2. oxytocin activity.
3. dopamine activity.
4. theory of mind.

Answers:

1. c, 2. c, 3. e, 4. a, 5. b, 6. b, 7. d, 8. d, 9. a, 10. a, 11. d, 12. b, 13. d, 14. c.

For Further Reading

1. *Possessing Genius: The Bizarre Odyssey of Einstein's Brain*, by Carolyn Abraham (St. Martin's, 2001), tells the story of the study of Einstein's brain and the controversy about how it came to be removed in the first place and about its caretaker, Thomas Harvey (coauthor of all the Einstein brain studies cited in this chapter).
2. "Representation of Number in the Brain," by Andreas Nieder and Stanislas Dehaene (*Annual Review of Neuroscience*, 2009, *32*, 185–208), reviews research on the basis of number understanding in children, adults, and nonhuman primates.
3. *Smarter: The New Science of Building Brain Power*, by Dan Hurley (Plume, 2014), describes scientists' efforts toward cognitive enhancement. James Flynn, noted writer on intelligence, remarks, "Anyone who doubts that environment can make a real difference to cognition should start with this book."
4. *Autism Spectrum Disorder*, by Jill Boucher (2nd ed., SAGE, 2017), describes our evolving understanding of the disorder.
5. *Thinking in Pictures: My Life With Autism* (Vintage, 2011) and *The Autistic Brain: Thinking Across the Spectrum* (Houghton Mifflin Harcourt, 2013), both by Temple Grandin, illuminate ASD as a disorder, along with the challenges of life with ASD.
6. *Born on a Blue Day: Inside the Extraordinary Mind of an Autistic Savant*, by Daniel Tammet (Free Press, 2006), chronicles his life, while his *Embracing the Wide Sky: A Tour Across the Horizons of the Mind* (Free Press, 2009) adds relevant scientific information.
7. *Attention-Deficit Hyperactivity Disorder*, edited by Russell Barkley (4th ed., Guilford Press, 2015), is a comprehensive treatment of ADHD in 35 chapters written by experts in the field.

Key Terms

attention-deficit/hyperactivity disorder (ADHD) 446

autism spectrum disorder (ASD) 438

autistic savant 445

default mode network 435

Down syndrome 437

fragile X syndrome 438

intellectual disability (ID) 436

intelligence 420

intelligence quotient (IQ) 420

phenylketonuria 438

theory of mind 439

Descriptions of Images and Figures

Back to Figure

The horizontal axis lists I Q score and percentile, tabulated below.

The labels for different I Q scores are as follows:

- 55 to 70: Retarded
- 100: Low average
- 115: High average
- 130 to 145: Gifted

The curve starts from the origin, peaks at I Q score equals 100, and falls.

Back to Figure

The problem shows three rows of rhombuses with three rhombuses in each row. This is followed by eight options, one of which is a solution. The color of the rhombuses is green and blue.

The pattern of the rhombuses in the problem is as follows.

- Row 1, column 1: The top left quarter is green.
- Row 1, column 2: The top right quarter is green.
- Row 1, column 3: The top half is green.
- Row 2, column 1: The bottom left quarter is green.
- Row 2, column 2: The bottom right quarter is green.
- Row 2, column 3: The bottom half is green.
- Row 3, column 1: The left half is green.
- Row 3, column 2: The right half is green.
- Row 3, column 3: Blank.

The pattern of the rhombuses in each numbered solution are as follows.

1. The top half is green.
2. The bottom half is green.
3. The bottom right quarter is green.
4. The top left quarter is green.
5. Each quarter of the rhombus is green.
6. The top left quarter, and the bottom right quarter is green.
7. The rhombus is blue.
8. The rhombus is green.

Back to Figure

The gray matter and white matter volumes are shown as highlighted regions. The data from the image are tabulated below.

Back to Figure

The horizontal axis is labeled Nerve conduction velocity groups and ranges from 1 to 5 in increments of 1. The vertical axis is labeled Mean I Q score, and ranges from 108 to 124 in increments of 2. The approximate data from the graph are tabulated below.

Back to Figure

The regions of activation are highlighted.

1. There are two sets of scans. The first scan is titled Calculations from memory, and the left prefrontal cortex is highlighted. The second scan is titled Estimation, and both the parietal cortices are highlighted.
2. There are two sets of scans, titled Easy calculation and Difficult calculation. Both scans show highlighted regions in the left and right prefrontal and parietal cortices. Smaller areas are shaded for Easy calculation and larger areas are shaded for Difficult calculation.
3. The scan is titled, Mental arithmetic. Larger areas of the left and right prefrontal and parietal cortices and some occipital areas are shaded.

Back to Figure

The horizontal axis is labeled I Q score relation, and ranges from 0 to 1, in increments of 0.2. The vertical axis lists familial relationships. The data from the graph are tabulated below.

Back to Figure

In the left and right hemispheres of identical twins, a large area of frontal, parietal, temporal lobes, somatosensory and motor areas, and Wernicke’s area show higher correlation in gray matter volume.

In the left and right hemispheres of fraternal twins, fewer areas of frontal lobe and somatosensory and motor areas show higher correlation in gray matter volume.

Back to Figure

The horizontal axis is labeled Infectious disease, and ranges from 2.0 to 5.0 in increments of 0.25. The vertical axis is labeled Average intelligence quotient, and ranges from 60 to 110 in increments of 5. The plots show a decreasing trend, plotted on either side of the best fit line between (2.0, 99) and (5.0, 66).

Back to Figure

The regions of activation are highlighted in the prefrontal cortex.

Young: Few regions of activity in the right hemisphere.

Old low: Larger regions of higher activity in the right hemisphere.

Old high: Regions of higher activity in both the hemispheres.

Back to Figure

1. The illustration shows 22 sets of chromosomes and a pair of X chromosomes. The length of the chromosomes decreases with increase in chromosome number. The divisions of the chromosomes are as follows.

    - 2 group: Chromosomes 1, 2, and 3
    - B group: Chromosomes 4 and 5
    - C group: Chromosomes 6, 7, 8, 9, 10, 11, and 12

- D group: Chromosomes 13, 14, and 15
- E group: Chromosomes 16 and 17.10
- F group: Chromosomes 19 and 20
- H group: Chromosomes 21 and 22

  All chromosomes, except the twenty first one, are in pairs. There are three twenty-first chromosomes.

2. The subjects of the documentary Born This Way at the red carpet during Emmys.

Back to Figure

The horizontal axis is labeled Year, and ranges from 2000 to 2016 in increments of 2. The vertical axis is labeled Prevalence in percentage, and ranges from 0 to 2 in increments of 0.2. The approximate data from the graph are tabulated below.

Back to Figure

The horizontal axis is labeled Age in years, and ranges from 3 to 35. The vertical axis is labeled Whole brain volume in centimeters cubed, and ranges from 1000 to 1600 in increments of 2000. The approximate data from the graph are tabulated below.

Back to Figure

The horizontal axis lists studies 1 through 5. The vertical axis is labeled relative odds of avoiding substance use disorder, and ranges from 0 to 9 in unit increments. The approximate data from the graph are tabulated below.

Back to Figure

1. The regions of cortical thinning are on the frontal-parietal area, anterior side of the temporal lobe, and parietal lobe.
2. White matter is reduced in the anterior-posterior pathway within the brain and around the ventricles.

14 PSYCHOLOGICAL DISORDERS

© iStockphoto.com/lolloj

Schizophrenia

Characteristics of the Disorder

Heredity

Two Types of Schizophrenia Symptoms

The Dopamine Hypothesis

Beyond the Dopamine Hypothesis

A Further Look | Antipsychotics and Their Side Effects

Neurological Anomalies in Schizophrenia

Concept Check

Affective Disorders

Heredity

The Monoamine Hypothesis of Depression

A Further Look | Targeting Drugs to Specific Receptors

Electroconvulsive Therapy

Antidepressants, ECT, and Neural Plasticity

Rhythms and Affective Disorders

Bipolar Disorder and Related Disorders

Neurological Anomalies in Affective Disorders

Suicide

Concept Check

Anxiety, Trauma, and Stress-Related Disorders

Heredity

Generalized Anxiety, Panic Disorder, and Phobia

Posttraumatic Stress Disorder

Anomalies in Brain Functioning

Concept Check

Personality Disorders

Obsessive-Compulsive Disorder

A Further Look | OCD and Mysophobia

OCD-Related Disorders (Grooming and Hoarding)

Borderline Personality Disorder

Concept Check

In Perspective

Chapter Summary

Study Resources

After reading this chapter, you will be able to

14.1 Name and describe the various categories of psychological disorders.

14.2 Understand the characteristics and neurological causes of schizophrenia.

14.3 Describe how heredity and environment interact to produce affective disorders.

14.4 Understand the symptoms and causes of the affective disorders.

14.5 Understand and describe the symptoms and physiological causes of the anxiety disorders.

14.6 Explain the causes and features of the major personality disorders.

Bob Garrett stood by his chair and waited for the students to take their places around the table, eagerly tying up the loose ends of conversations that the trek across campus hadn't given them time to finish. As the bell in the East College tower tolled the start of the hour and he was about to call the class to order, Ned got up from his seat and approached him.

"I forgot to give the bookstore cashier her pen after I used it to write a check. Can I take it back?"

"I think she can wait until class is over," Bob answered. Ned accepted that judgment and returned to his seat, but he seemed restless for the remainder of the hour. As soon as class was over, he was one of the first out of the door. Bob couldn't help but smile at Ned's youthful impetuousness.

The next day, he understood that Ned's behavior had a completely different origin. Around 10 o'clock the night before, Ned's dorm mates had found him huddled on the stair landing, fending off an imaginary alien spaceship circling over his head and firing projectiles at him. He was taken to the hospital and sedated; then his parents took him back to his hometown, where he spent several months in a hospital psychiatric ward. He was diagnosed with paranoid schizophrenia. Fortunately, medication helped, and he was able to move to a home school with a comprehensive program of support and rehabilitation.

Ned has now spent two thirds of his life at the home. A few years ago, he wrote to Bob, and they have kept up a regular correspondence since; his primary motivation is that he remembers his brief time in college as the happiest in his life. It is not that the home is unpleasant. He is on the baseball, basketball, and golf teams; he works part-time outside the home; and he has a girlfriend. Questions he asks in his letters reveal a healthy curiosity, usually provoked by something he has read or seen on television about the brain. Once he talked candidly about his diagnosis and about how he prefers to believe that someone slipped him a dose of LSD on that fateful night. There is no evidence that happened, but even if it did, it only precipitated, rather than caused, the decades-long debilitation that followed. Despite Ned's apparently good adjustment—and we see only the face that he wants to put on his situation—the preadolescent intellectual maturity of his letters and the barely legible scrawl of his handwriting suggest the havoc that schizophrenia has wreaked in his brain. Ned is unable to function outside the home's protective environment and professional support, and he will never be able to leave.

Researchers estimate that one out of every five adults in the United States lives with a diagnosable mental illness (Figure 14.1; National Institute of Mental Health, 2019a) and that 46% will fall victim during their lifetime (Kessler et al., 2005). We aren't sure how many people have mental illness, because researchers rely primarily on self-reports, which are notoriously inaccurate. In late-life interviews, people recalled bouts of mental illness 2 to 12 times less often, depending on the type of illness, than they had reported them in three interviews over the previous 25 years (Takayanagi et al., 2014). The monetary cost in terms of treatment and lost wages amounts to $467 billion per year in the United States (Insel, 2015) and $2.5 trillion globally (S.

Trautmann, Rehm, & Wittchen, 2016). Mental and behavioral disorders are the third leading cause of disability in the United States, after cardiovascular disease and cancer (U.S. Burden of Disease Collaborators, 2013). An obvious benefit of research is the development of improved therapeutic techniques; in addition, because the disorders involve malfunctions in neurotransmitter systems and brain structures, studying them helps researchers understand normal neural functioning as well. In this chapter, we will make good use of what you have already learned about brain structure and neurotransmitter activity as we examine schizophrenia, mood disorders, anxiety disorders, and personality disorders; in turn, this will further expand your knowledge of how the brain works.

Figure 14.1 Psychological Disorders Impair a Person's Ability to Cope.

Source: Cheryl Chan/Moment/Getty.

The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM*-5; American Psychiatric Association, 2013), provides the framework for therapists, clinicians, and researchers in assessing an individual's unique history and symptoms and arriving at a diagnosis from a long list of disorders (for example, see Table 14.1). Many of these disorders have been discussed in prior chapters, such as substance-related disorders (Chapter 5), eating disorders (Chapter 6), sexual and gender dysfunctions (Chapter 7), aggressive and disruptive disorders (Chapter 8), and neurodevelopmental and cognitive disorders (Chapters 12 and 13). This chapter will focus on several of the remaining disorders: schizophrenia spectrum disorders, affective disorders, anxiety disorders not covered in Chapter 8, and personality disorders.

Table 14.1

But before we start, we should probably discuss two terms you'll see a lot in this chapter and in press articles as you go forward with your career: incidence and prevalence. **Incidence** is defined as the number of individuals who develop a condition across a specific amount of time (usually a year). **Prevalence**, on the other hand, is the total count (or percentage) of people with a condition at a specific point in time.

SCHIZOPHRENIA

Schizophrenia is a debilitating disorder characterized by perceptual, emotional, and intellectual deficits that include loss of contact with reality and an inability to function in life. Schizophrenia is a **psychosis**, which simply means that the individual has severe disturbances of reality, orientation, and thinking. Schizophrenia is the most severe of the mental illnesses, and it is particularly disruptive because of the bizarre behavior it produces in many of its victims. All social classes are equally vulnerable; though patients themselves "drift" to lower socioeconomic levels, when they are

TABLE 14.1 Major Forms of Mental Disorders.

DISORDER	SYMPTOMS
Schizophrenia	Perceptual, emotional, and intellectual deficits; positive and negative symptoms
Affective Disorders	
Major depressive disorder (MDD)	Sadness, hopelessness, decreased enjoyment, loss of energy and appetite, slow thought, sleep disturbance
Bipolar disorder (I or II)	Alternating depression and either anxiety, irritation, or mania
Seasonal affective disorder (SAD)	Depression that worsens in the winter and improves in the summer
Anxiety, Trauma, and Stress-Related Disorders	
Generalized anxiety disorder	Feeling of stress and unease most of the time
Panic disorder	Sudden and intense attack of anxiety with no obvious trigger
Phobia	Fear or stress when confronted with a particular situation
Posttraumatic stress disorder (PTSD)	Prolonged stress reaction to a stressful event characterized by recurrent thoughts, images, nightmares, impaired concentration, and overreaction to sudden events
Personality Disorders	
Obsessive-compulsive disorder (OCD)	Recurrent, uncontrollable thoughts (obsessions) paired with ritualistic behaviors that remove anxiety (compulsions)
Hoarding disorder (HD)	Obsessive collection of objects (regardless of value) and an inability to throw them away, leading to stress and impairing daily life
Tourette syndrome	Involuntary motor and sound tics, grimaces, blinks, grunts, and imitation
Borderline personality disorder	Unstable mood, self-image, anxiety, self-harm, and anger that leads to impulsive acts due to apparently common events

classified by their parents' socioeconomic level, the classes are proportionately represented (Huber, Gross, Schüttler, & Linz, 1980). The global prevalence of psychotic disorders across 101 studies from 1990 to 2015 was 0.39% to 0.46% of the population; in the United States the rate is 0.65%, or roughly 2.1 million people (Moreno-Küstner, Martin, & Pastor, 2018). The economic burden of schizophrenia amounts to $156 billion annually in the United States, which includes direct healthcare costs (24%), unemployment (38%), and caregiving (34%; Cloutier et al., 2016). Suicide is a major concern; almost 10% of individuals with schizophrenia try to take their own life at some point, with young sufferers at highest risk (Zaheer et al., 2018).

Fortunately, schizophrenia is one of the few psychological disorders that appear to be on the decline. Critics have attributed the apparent reduction to methodological flaws in studies, but a study of all people born in Finland between 1954 and 1965 found a significant decline in each successive age-group, totaling 29% for women and 33% for men (Suvisaari, Haukka, Tanskanen, & Lönnqvist, 1999). This decrease has been noted in other countries such as Japan (Toshitani et al., 2006) and the United States (Moreno-Küstner et al., 2018). Surprisingly, there is evidence that the disorder might be on the rise in Canada (Dealberto, 2013).

Characteristics of the Disorder

The term *schizophrenia* was coined in 1911 by the Swiss psychiatrist Eugen Bleuler (Figure 14.2) from the combination of two Greek words meaning "split mind." Contrary to popular belief, schizophrenia has nothing to do with multiple personalities; the term refers to the distortion of thought and emotion, which are "split off" from reality. The person with schizophrenia has some combination of several symptoms: hallucinations (internally generated perceptual experiences, such as voices telling the person what to do); delusions (false, unfounded beliefs, such as that one is a messenger from God); disorganized thought; inappropriate emotions or lack of emotion; and social withdrawal. Note that Ned had a hallucination of a spaceship, the paranoid delusion that it was attacking him, and a possible delusion about the LSD.

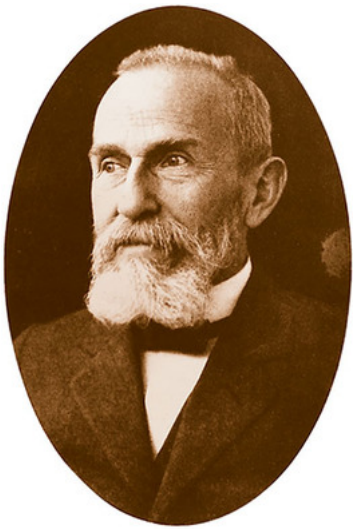
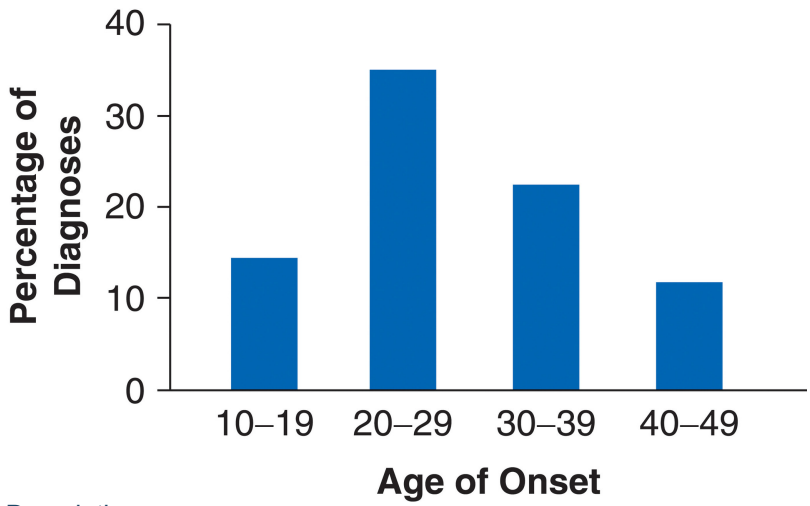


Figure 14.2 Eugen Bleuler (1857–1939).
A pioneer in the field, he introduced the term *schizophrenia*.

Source: © Bettmann/Getty Images.

In the past, people with schizophrenia were also subdivided into diagnostic categories based on which of these symptoms was predominant, such as *paranoid* or *catatonic*. However, patients often have overlapping symptoms and can receive multiple diagnoses, so there is little belief that these categories represent distinct disease processes. Also, as neuroscience and evidence-based practices progress, we understand that two people can have the same symptom with different causes or the same brain defect with different symptoms. As a result, the National Institute of Mental Health encourages researchers and clinicians to shift their focus from diagnostic categories to underlying neural and genetic mechanisms (G. Miller, 2010). As a first step in that direction, the *DSM*-5 eliminated these subgroups of schizophrenia as diagnostic categories (American Psychiatric Association, 2013).

Schizophrenia afflicts men and women about equally often, and there is no difference in incidence between urban and rural environments (Saha, Chant, & McGrath, 2005). Men usually show the first symptoms during their teens or twenties, as Ned did, while the onset for women ordinarily comes about a decade later (Figure 14.3). **Acute** symptoms develop suddenly and are typically more responsive to treatment; the prognosis is reasonably good, despite brief relapses. Symptoms that develop gradually and persist for a long time with poor prognosis are called **chronic**. One example of chronic changes occurs in language: Subtle but significant changes in language, such as vagueness in concepts, might indicate the early development of symptoms before the more severe symptoms develop months or years later (Rezaii, Walker & Wolff, 2019). The media has frequently overplayed the bizarre features of schizophrenia; many patients are able to function reasonably well, especially if they are fortunate enough to be among those who respond to antipsychotic drugs. Among patients studied 20 years after their first psychiatric admission, 22% were fully recovered, another 43% were improved, and the symptoms of the remaining 35% had remained the same or worsened; 56% were fully employed (Huber et al., 1980). A more recent meta-analysis of 79 studies performed by Lally and colleagues (2017) is consistent with this earlier study (38% in remission after 7 years).



Description

Figure 14.3 Risk for Schizophrenia by Age.

Source: Data from Huber et al. (1980).

In the late 1700s and early 1800s, doctors began to view mental illness as a medical problem; at that time, those with mental illness were literally released from their chains and given treatment (Figure 14.4; Andreasen, 1984). By the early 20th century, it was widely assumed that schizophrenia had a physiological basis. But when the search for biological causes produced little success, the emphasis shifted in the 1940s to the social causes of schizophrenia, especially in the United States, where Freud's theory of psychoanalysis was in its ascendancy and biologically oriented psychiatrists were in the minority (Andreasen, 1984; Wender, Rosenthal, Kety, Schulsinger, & Welner, 1974). Until the 1960s, research techniques were not up to the task of demonstrating the validity of the physiological position. It was then that increasing knowledge of neurotransmitters, the advent of brain-scanning techniques, and improved genetic studies shifted the explanation for schizophrenia back to the realm of biology and permanently changed the perception of mental illness.

Figure 14.4 Philippe Pinel Freeing Mental Patients From Their Chains.
Patients were warehoused without treatment; care sometimes consisted solely of throwing in fresh straw and food once a week. Pinel was convinced that they would benefit from humane treatment, and in 1794 freed the mental patients of Paris from their chains.

Source: Stock Montage / Contributor / Getty Images.

Heredity

Schizophrenia is a familial disorder, which means that the incidence of schizophrenia is higher among the relatives of people with schizophrenia than it is in the general population (Gottesman, McGuffin, & Farmer, 1987; Tsuang et al., 1991). Of course, this association could be due to environmental influence or to heredity; in fact, in the 1940s, supporters for both the genetic and environmental bases argued for their positions from the same data (Wender et al., 1974). However, studies of twins and adoptees provided compelling evidence for a genetic influence.

Twin and Adoption Studies

In Figure 14.5, you can see that the shared incidence of schizophrenia increases with the genetic closeness of the relationship and that the concordance rate for schizophrenia is three times as high in identical twins as in fraternal twins (Lenzenweger & Gottesman, 1994). In other words, identical twins of people with schizophrenia are three times as likely to develop the disorder as the fraternal twins of patients. The heritability for schizophrenia has been estimated at around .80 (Cardno & Gottesman, 2000; Sullivan, Kendler, & Neale, 2003). This means that 32% of the variability is due to environmental factors.

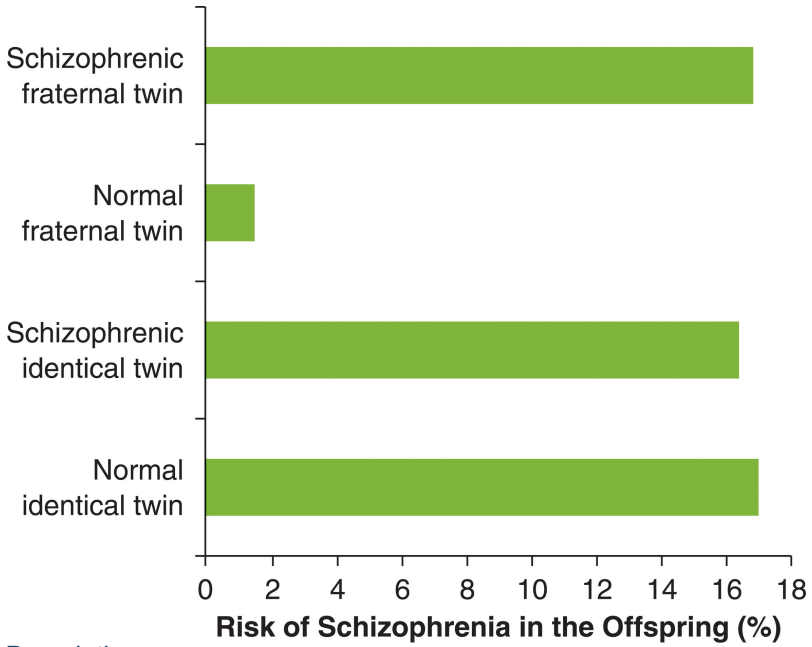
Genetic Relatedness	Relationship	Risk
100%	Identical twin	48%
100%	Offspring of two patients	46%
50%	Fraternal twin	17%
50%	Offspring of one patient	17%
50%	Sibling	9%
25%	Nephew or niece	4%
0%	Spouse	2%
0%	Unrelated person in the general population	1%

Description

Figure 14.5 Concordances for Schizophrenia Among Relatives.
Source: Introduction to Psychology, Gateways to Mind and Behavior (with InfoTrac), 11th edition by D. Coon and John O. Mitterer, 2007. Reprinted with permission of Wadsworth, a division of Thomson Learning. Estimates from Lenzenweger & Gottesman, 1994.

Information from adoption studies gives a more impressive indication of genetic influence; these studies show that adopting out of a home with schizophrenia provides little or no protection from developing schizophrenia symptoms. The incidence of schizophrenia *and* schizophrenia-like symptoms was 28% among individuals adopted out of Danish homes in which there was one parent with schizophrenia, compared with 10% in matched adoptees from homes without an individual with symptoms (Lowing, Mirsky, & Pereira, 1983). Other studies have produced similar findings.

Discordance among identical twins has been used as an argument that schizophrenia is environmentally produced. To address this issue, Gottesman and Bertelsen (1989) compared the incidence of schizophrenia in the offspring of affected and normal identical twins; they found that the offspring of the unaffected identical twins were just as likely to have schizophrenia as the offspring of the affected twins (Figure 14.6). This result would not have occurred unless the normal twins were carrying genes for schizophrenia. Discordance does raise the question, however, of whether some environmental factors determine whether the person's schizophrenic genes will remain "silent." Refer back to Chapter 6 for the discussion of these *epigenetic* effects on genes.



Description

Figure 14.6 Risk of Schizophrenia in the Offspring of Normal Twins and Twins With Schizophrenia.
Offspring of the normal fraternal twin of an individual with schizophrenia do not have an elevated risk. The offspring of the normal identical twin of an individual with schizophrenia are as likely to show symptoms as the offspring of the identical twin with schizophrenia.

Source: Based on data from Gottesman and Bertelsen (1989).

The Search for the Schizophrenia Genes

Although we have known for a long time that schizophrenia is partially genetic, identifying the genes involved has been difficult. One reason has been researchers' inconsistency in including the spectrum disorders in their diagnosis of schizophrenia (Heston, 1970; Lowing et al., 1983). When identical twins are discordant for schizophrenia, 48% to 54% of the nonschizophrenic twins have spectrum disorders (Heston, 1970; Onstad, Skre, Torgersen, & Kringlen, 1991). If the spectrum disorders are due to the same genes, then classifying these individuals as nonschizophrenic means that the genes will not appear to distinguish between schizophrenia and normality. A second problem is that schizophrenia apparently involves the cumulative effects of multiple genes, each of which has a small effect by itself. Evidence indicates that the number of variants contributing to schizophrenia is in the thousands (Wray & Visscher, 2010). A person's risk of schizophrenia presumably increases with the number of these genes inherited. This view is supported by the fact that risk has

been found to increase with the number of relatives who have schizophrenia and with the degree of the relatives' disability (Heston, 1970; Kendler & Robinette, 1983).

Recent genome-wide studies have identified at least 108 genes suspected of a role in producing schizophrenia (Schizophrenia Working Group, 2014; Thyme et al., 2019). These genes are typically related to neurodevelopment and plasticity of the forebrain, neurotransmission (such as dopamine, glutamate, and calcium channels), immune and stress responses, and hormonal activity such as the *DISC1* (disrupted in schizophrenia 1) gene. This gene appears to change how neurons develop and migrate by disrupting a messenger system in neurons in areas involved in learning, memory, and mood (J. Y. Kim et al., 2009; Millar et al., 2000; Millar et al., 2005). Although many genes such as *DISC1* and *22q11.2* have been linked to schizophrenia, they have small individual effects and together may account for less than 5% of the variability in susceptibility. Copy number variations (CNVs) have much larger effects; for example, a duplication of a segment of DNA on chromosome 7 produces a 10-fold increase in risk (Mulle et al., 2014). But specific CNVs are individually rare and make an even smaller contribution than common genes. The large majority of CNVs are inherited, but *de novo* mutations are more often implicated in diseases. Along with epigenetic modifications, they help account for discordance in identical twins, who otherwise have identical genomes. Epigenetic studies of schizophrenia are in their infancy. Though they have produced interesting results, our knowledge is based on small numbers of subjects and tissues taken from widely varying brain locations. According to one group of reviewers, some of the current results may be harder to interpret than early small-sample gene association studies (Dempster, Viana, Pidsley, & Mill, 2013).

Schizophrenia is a very old disease (see W. J. Ray, 2014, for a review). Disorders with psychotic-like symptoms have been reported for 4,000 years, and similar rates in disparate and long-separated societies suggest that the genes originated sometime between our evolutionary divergence from Neanderthals and the time humans left Africa some 100,000 years ago (Gulsuner et al., 2020; Srinivasan et al., 2016). So why wouldn't genes as detrimental as those that produce schizophrenia be eliminated through evolution? One suggestion is that the genes that in combination can produce schizophrenia individually confer an evolutionary advantage. Ten or fifteen centuries ago, these individual genes might have helped individuals cope with the demands of a burgeoning social culture that valued creativity and communication (Srinivasan et al., 2016). An individual's overall risk for schizophrenia (as well as for bipolar disorder) is highly correlated with intellectual and artistic creativity (Power et al., 2015), and it has been pointed out that many gifted Nobel recipients, the likes of Albert Einstein, Bertrand Russell, and John Nash (featured in the film *A Beautiful Mind*), either had some schizophrenic traits or had relatives thought to have schizophrenia. Apparently our amazing human ability to express, integrate, and create comes with an increased risk for psychotic disorders that can be triggered by the same genes and circuits.

The Vulnerability Model

Most researchers agree that genes determine only the person's vulnerability for the illness; both heredity and environment are needed to explain the *etiology* (causes) of schizophrenia (Zubin & Spring, 1977) as well as most other disorders. According to the **vulnerability model**, some threshold of causal forces must be exceeded for the illness to occur; environmental challenges combine with a person's genetic vulnerability to exceed that threshold. The environmental challenges may be external, such as bereavement, job difficulties, or divorce, or they may be internal, such as maturational changes, poor nutrition, infection, or toxic substances. We see increased incidences in urban settings compared to rural ones, which suggests that overcrowding and urban pollution increase an individual's vulnerability to the disorder (J. McGrath & Saha, 2008). There is mounting evidence that these environmental influences work in part by epigenetic means, that is, by upregulating and downregulating gene functioning (Tsankova, Renthal, Kumar, & Nestler, 2007). Vulnerability is viewed as a continuum, depending on the number of affected genes inherited. At one extreme, a small percentage of genetically predisposed individuals will become schizophrenic under the normal physical and psychological stresses of

life; at the other extreme are individuals who will become schizophrenic only under the severest stress, such as the trauma of battle (Fowles, 1992), or because of a constantly stressful life with poor social support and family environments (see C. Lange et al., 2017).

Two Types of Schizophrenia Symptoms

Researchers disagree on whether schizophrenia represents one disease or many, but most authorities do agree that the symptoms fall into two major categories: positive and negative. **Positive symptoms** involve the presence or exaggeration of behaviors, such as delusions, hallucinations, disorganized thinking, and abnormal motor behaviors. **Negative symptoms** are characterized by the absence or insufficiency of normal behaviors and include lack of affect (emotion), inability to experience pleasure, lack of motivation, poverty of speech, and impaired attention and social interactions.

Positive symptoms are more often acute, and they are more likely to respond to antipsychotic drugs than are negative symptoms (D. C. Fowles, 1992). Negative symptoms tend to be chronic; these patients show poorer adjustment prior to the onset of the disease (Andreasen, Flaum, Swayze, Tyrrell, & Arndt, 1990); poorer prognosis after diagnosis (Dollfus et al., 1996); more intellectual and other cognitive deficits, suggestive of a brain disorder (Andreasen et al., 1990); and greater reduction in brain tissue (D. C. Fowles, 1992). Positive and negative symptoms are described in Table 14.2. These findings led researchers to think in terms of two distinct groups of patients, but, in fact, many patients have at least some symptoms of both types, and schizophrenia often begins with positive symptoms and transitions over time to predominantly negative symptoms.

Table 14.2

TABLE 14.2 Positive Versus Negative Schizophrenia Symptoms.

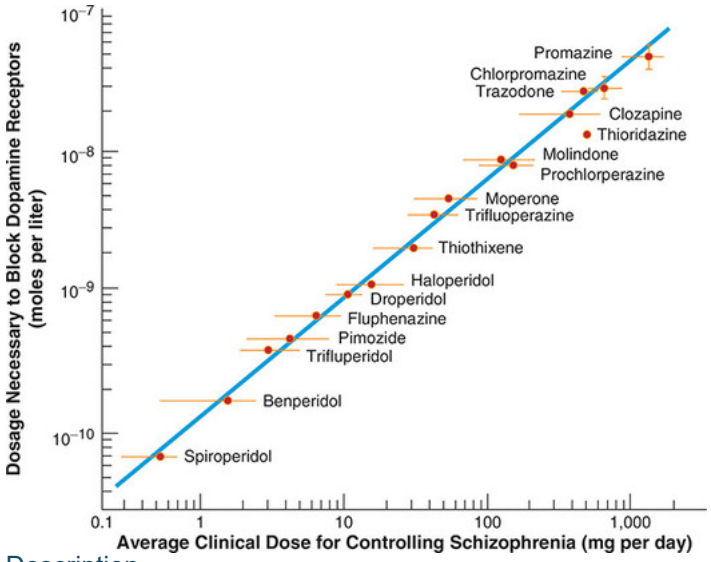
ASPECT	TYPE I (POSITIVE)	TYPE II (NEGATIVE)
Symptoms	Delusions, hallucinations, agitation, bizarre behavior, etc.	Poverty of speech and thought, lack of emotion, apathy, feelings of emptiness
Treatment	Antidopaminergic drugs	Increasing glutamate signaling
Timetable of recovery	Potentially reversible	Long-term
Intellectual impairment	Absent	Sometimes present
Suggested pathological process	Increased D_2 dopamine receptors	Cell loss in temporal lobes, decrease in glutamate signaling

The Dopamine Hypothesis

Little could be done to treat psychotic patients until the mid-1950s, when a variety of antipsychotic medications arrived on the scene. For the first time in history, the population of hospitalized mental patients decreased in size. As is often the case in medicine, and more particularly in mental health, these new drugs had not been designed for this purpose—researchers had too little understanding of the disease to do so. Doctors tried chlorpromazine with a wide variety of mental illnesses because it calmed surgical patients, and it turned out to help those with schizophrenia as well. However, it was not clear *why* chlorpromazine worked, because tranquilizers have little or no usefulness in treating schizophrenia.

So investigators tried reverse engineering. You will remember from Chapter 5 that amphetamine overdose causes psychotic behavior indistinguishable from schizophrenia, complete with hallucinations and paranoid delusions. In time, researchers determined that amphetamine produces these symptoms by increasing dopaminergic activity. This discovery eventually led to the **dopamine hypothesis** : that schizophrenia involves excessive dopamine activity in the brain. According to the

theory, blockade of the D_2 subtype of dopamine receptors is essential for a drug to have an antipsychotic effect, and a drug's effectiveness is directly related to the drug's blocking potency. The theory has considerable support; patients with schizophrenia typically have higher dopamine activity in the striatum, and drugs that block dopamine receptors are effective in treating the positive symptoms of schizophrenia (Toda & Abi-Dargham, 2007). In fact, the effective dosage for most antipsychotic drugs is directly proportional to their ability to block dopamine receptors (Figure 14.7; Seeman, Lee, Chau-Wong, & Wong, 1976). What exactly does dopamine do to trigger the symptoms of schizophrenia? One theory, called the **aberrant salience hypothesis**, suggests that heightened levels of dopamine increase attentional and motivational circuits to make ordinary environmental features seem significant. Therefore, an individual projects his or her own thoughts and imaginings as real-world events and experiences (Howes & Nour, 2016).



Description

Figure 14.7 Relationship Between Receptor Blocking and Clinical Effectiveness of Schizophrenia Drugs.
The horizontal axis is the average daily dose prescribed by physicians; the horizontal red lines represent typical ranges of doses used. Values on the vertical axis are amounts of the drug required to block 50% of the dopamine receptors.

Source: Reprinted by permission from "Antipsychotic Drug Doses and Neuroleptic/Dopamine Receptors," by P. Seeman et al., *Nature, 261,* p. 718, fig. 1. Copyright 1976 Macmillan Publishers, Ltd.

Beyond the Dopamine Hypothesis

However, the drugs did not help 30% to 40% of patients with schizophrenia, and—troublesome for the dopamine theory—nonresponsive patients experienced just as much D_2 receptor blockade as responders. In fact, in some of them, the blockade exceeded 90%, while some responders showed remarkably low levels of receptor blocking (Kane, 1987; Pilowsky et al., 1993). Furthermore, some patients appear to have a *dopamine deficiency*, especially those with chronic, treatment-resistant symptoms (Heritch, 1990; Okubo et al., 1997).

Another problem for the drugs was that the side effects could be permanently disabling. Prolonged use of dopamine-blocking drugs often produces **tardive dyskinesia**, tremors and involuntary movements due to long-term blocking of dopamine receptors and resultant neuron death in the basal ganglia. Once dyskinesia develops, it persists even after the person stops taking the drug. Seventy years ago, this effect was believed to be so inevitably linked to the therapeutic benefit that the "right" dose was the one that caused some degree of motor side effects. Thus, the

drugs used to treat schizophrenia became known as **neuroleptics**, because the term means “that which takes (control of) the nerve” (C. King & Voruganti, 2002). The effect appears to be due to a compensatory increase in the sensitivity of D_2 receptors in the basal ganglia. (This is a good illustration of the fact that drugs do not affect just the part of the brain we want to treat.) These debilitating side effects, along with the ineffectiveness of dopamine blockers with some patients, led researchers both to question the dopamine hypothesis and to look for new approaches.

Since the early 1990s, we have seen the introduction of numerous new antipsychotic substances that are referred to as *atypical* or *second-generation* drugs. Atypical antipsychotics block D_2 receptors less strongly, while also targeting non-dopamine receptors; as a result, they produce tardive dyskinesia only at much higher doses, but they still reduce psychotic symptoms. Fortunately, avoiding motor side effects does not require a therapeutic compromise. Atypical antipsychotics are at least equivalent to the first-generation drugs, and some, such as clozapine, are 15% to 25% more effective; what is more, they have fewer side effects, and they often bring relief to treatment-resistant patients (Pickar, 1995; Samara et al., 2016). So is the dopamine hypothesis just another example of a beautiful hypothesis slain by ugly facts? Not entirely; although atypical antipsychotics mostly target other receptors, those that lack at least a modest effect at D_2 receptors are therapeutically ineffective (Correll, 2010; H. M. Jones & Pilowsky, 2002). So successful therapy apparently requires D_2 blockade *and* other effects. A Further Look summarizes the types of drugs prescribed for schizophrenia and their side effects.

A Further Look:

Antipsychotics and Their Side Effects

First-generation antipsychotic (FGA) drugs include Thorazine (chlorpromazine) and Haldol (haloperidol). Potent D_2 blockers, they help alleviate positive symptoms in most individuals with schizophrenia. They have three major categories of side effects (J. D. Preston, O’Neal, & Talaga, 2017). The first and most severe are called extrapyramidal effects and are a result of excessive blocking of dopamine receptors; impaired movement such as tardive dyskinesia, shuffling gait, tremors, and a blank facial expression are a result of damage to the basal ganglia (the “extrapyramidal” region) and mimic Parkinson’s disease. Although extrapyramidal effects are immediately apparent with FGAs, the tardive dyskinesia is seen only after prolonged use and is common for Haldol. The second group of side effects are anticholinergic and are due to blocking acetylcholine receptors and the parasympathetic nervous system. These include dry mouth and eyes, constipation, and sedation. Antiadrenergic side effects, the third group, are caused by blocking the sympathetic nervous system and result in low blood pressure and lightheadedness. Both the second and third categories are common side effects of Thorazine.

Second-generation antipsychotic (SGA) drugs include clozapine, Risperdal (risperidone), Latuda (lurasidone), Zyprexa (olanzapine), Rexulti (brexpiprazole), Vraylar (cariprazine), and Seroquel (quetiapine). They weakly block D_2 receptors but strongly block serotonin 5-HT_{2A} receptors, which helps with the negative symptoms of schizophrenia. Because dopamine is not strongly blocked, there is a much smaller risk of extrapyramidal effects, including tardive dyskinesia. However, these drugs carry their own set of undesirable side effects. They tend to cause sleepiness, can result in weight gain, and in rare cases can cause heart problems. Two major side effects that rarely occur are agranulocytosis, a life-threatening blood disorder (Idänpään-Heikkilä, Alhava, Olkinuora, & Palva, 1977), and serotonin syndrome, which causes sweating, high body temperature, seizures, headaches, and confusion (Buckley, Dawson, & Isbister, 2014). Both are life threatening and must be treated immediately by administration of either blood factors (for agranulocytosis) or serotonin agonists (for serotonin syndrome).

Second-generation antipsychotics have been around for almost 50 years, so when will third-generation drugs be released? Some say they already exist, and Abilify

(aripiprazole) is sometimes listed as an example. This drug appears to be a dopamine stabilizer, similar to bipolar drugs that stabilize mood (Mailman & Murthy, 2010). Other drugs in this group might be highly selective for only a subset of receptor types, so that they are effective without the side effects of the drugs that have broader effects.

And what are these non-dopaminergic effects of atypical antipsychotics? One involves serotonin. The serotonergic system is suspected largely because of the schizophrenic-like responses to hallucinogenic drugs, such as psilocybin and LSD, which affect 5-HT_{2A} receptors. The number of 5-HT_{2A} receptors is upregulated in the brains of deceased subjects with schizophrenia (González-Maeso et al., 2008), and atypical antipsychotics block serotonin 5-HT_2 receptors by as much as 95% (Correll, 2010).

But serotonin has not received nearly as much attention as glutamate, which is the major excitatory neurotransmitter in the brain and is also affected by atypical antipsychotics. The drugs phencyclidine (PCP, also called angel dust) and ketamine, which inhibit the NMDA (*N*-methyl-d-aspartic acid) subtype of glutamate receptor, mimic schizophrenia far better than amphetamine does, particularly in producing both negative and positive symptoms (Sawa & Snyder, 2002). The amino acid glycine activates the NMDA receptor, and adding it (or similar compounds) to antipsychotic medications reduces both kinds of symptoms (Hirayasu et al., 2016; Lisman et al., 2008). According to the **glutamate theory**, hypofunction of NMDA receptors results in increases in glutamate and downstream increases in dopamine, which together produce positive and negative symptoms of schizophrenia (Lisman et al., 2008; Sendt, Giaroli, & Tracy, 2012). Indeed, genes that underlie glutamate signaling are correlated with the severity of schizophrenia and related disorders (N. L. O'Brien et al., 2014; Saini et al., 2017). Glutathione, a compound in the brain that contains glutamate, is reduced in the brains of people with schizophrenia; when volunteers took sulforaphane for 7 days, it increased glutathione in their brains (Sedlak et al., 2017). Sulforaphane is abundant in broccoli and cabbage, so your mom was right when she told you to eat your vegetables! However, it has been difficult to develop drugs that target NMDA receptors or reduce glutamate levels and that are both therapeutically effective and well tolerated (Sendt et al., 2012). All potential drugs to date have been unsuccessful in clinical trials.

Obviously, it would be a mistake to focus entirely on a single neurotransmitter, considering the complex interactions among them. The glutamate theory provides some recognition of this fact, and it is showing considerable usefulness in explaining schizophrenia and some promise in guiding drug development. While we wait for the glutamate story to unfold, and for a more holistic understanding of the complex interactions of the various implicated neurotransmitters, we have additional clues about the origins of schizophrenia from structural and functional anomalies in the brain.

Neurological Anomalies in Schizophrenia

Malfunctions have been identified in virtually every part of the brain in people with schizophrenia. The most consistent finding has been enlargement of the ventricles, indicating a loss of gray matter; a second is hypofrontality, or reduced activity in the frontal lobes. We will examine each of these defects in turn.

Brain Tissue Deficits and Ventricular Enlargement

A signature characteristic of schizophrenia is a decrease in brain tissue, both gray and white matter, with deficits reported in at least 50 different brain areas (Honea, Crow, Passingham, & MacKay, 2005). The number of sites and the variability across studies attest to the multifaceted nature of schizophrenia, but the frequency with which deficiencies are found in the frontal and temporal lobes indicates that they are particularly important. These tissue losses are accompanied by alterations in neural functioning but not necessarily in the expected direction: Activity is decreased in the

dorsolateral prefrontal cortex but increased in the orbitofrontal cortex and in a subregion of the hippocampus (Schobel et al., 2009). In fact, the hippocampal activation is so characteristic of schizophrenia that in a group of people having brief psychotic symptoms, it identified with 70% accuracy those who would later be diagnosed with full-blown schizophrenia (Schobel et al., 2009).

? What brain defects have been found in schizophrenia?

An indication of the tissue deficits seen in schizophrenia is ventricular enlargement; this is because the ventricles expand to take up space normally occupied by brain cells (Figure 14.8). Both deficiencies are usually subtle, on the order of less than a tables poonful increase in ventricular volume (Suddath et al., 1989) and a 2% decrease in brain volume (Haijma et al., 2012; Harrison, Freemantle, & Geddes, 2003), but these figures belie the functional importance of the losses. In fact, an often-distinguishing feature between identical twins discordant for schizophrenia is the size of their ventricles (Suddath, Christison, Torrey, Casanova, & Weinberger, 1990). Ventricular enlargement is not specific to schizophrenia; enlarged ventricles are also associated with several other conditions, including old age, dementia (loss of cognitive abilities), Alzheimer's disease, Huntington's chorea (Weinberger & Wyatt, 1983), and alcoholism with dementia (D. M. Smith & Atkinson, 1995). Nor are enlarged ventricles an inherent characteristic of schizophrenia (Davatzikos et al., 2020). As you can see in Figure 14.8a, several controls have enlarged ventricles, and many of the patients have ventricle sizes in the normal range. We will look more closely at the tissue deficits later when we consider their origins.

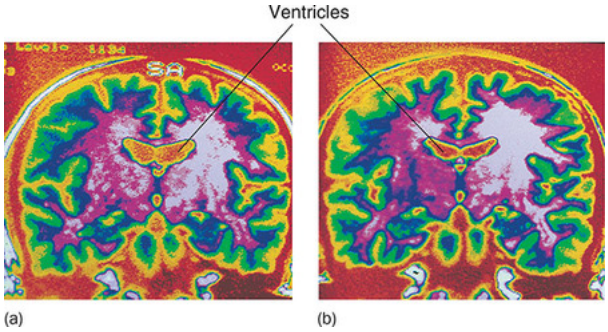


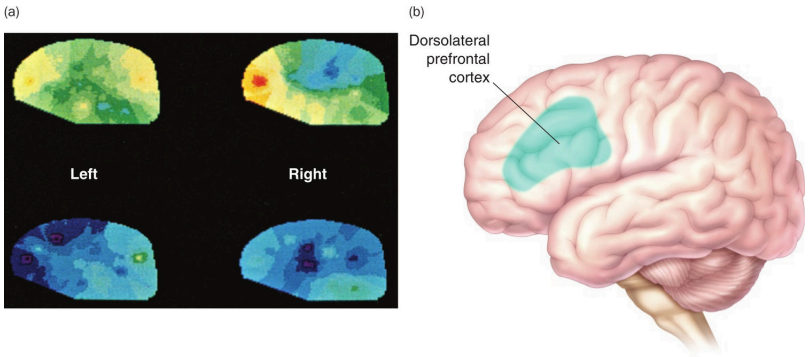
Figure 14.8 Ventricle Size in People With and Without Symptoms of Schizophrenia. In two identical twins, (a) the lateral ventricles are larger in the one with schizophrenia (left). However, (b) shows that while this difference is true on average (indicated by the dotted lines), lateral ventricle size is normal in several patients and larger in several controls.

Sources: (a) Copyright 1990 Massachusetts Medical Society. All rights reserved. (b) From "Lateral Cerebral Ventricular Enlargement in Chronic Schizophrenia," by D. R. Weinberger et al., *Archives of General Psychiatry, 36,* pp. 735–739. Copyright 1979 American Medical Association.

Hypofrontality

Earlier, we saw that prefrontal functioning can be assessed by using the gambling task; an alternative technique is the **Wisconsin Card Sorting Test**, which requires individuals to change strategies in midstream, first sorting cards using one criterion but then changing to another. Many people with schizophrenia perform poorly on the test, persisting with the previous sorting strategy. Normal individuals show increased activation in the prefrontal area during the test; patients with schizophrenia typically do not, despite normal activation in other areas (Weinberger, Berman, & Zec, 1986). Figure 14.9 shows a normal brain practically lighting up during the test, in comparison with the schizophrenic brain, especially in the frontal area called the *dorsolateral prefrontal cortex*. This hypofrontality during the Wisconsin Card Sorting Test has been attributed to disrupted communication between the hippocampus and the prefrontal

cortex (Weinberger, Berman, Suddath, & Torrey, 1992). It also apparently involves prefrontal dopamine *deficiency*, because administering amphetamine increases blood flow in the prefrontal cortex and improves performance on the Wisconsin Card Sorting Test (Daniel et al., 1991). Traumatic injury to the dorsolateral prefrontal cortex causes impairments like the symptoms of schizophrenia: flat affect, social withdrawal, reduced intelligence and problem-solving ability, diminished motivation and work capacity, and impaired attention and concentration (Weinberger et al., 1986). Because of the frontal lobes' involvement in planning actions, recognizing the consequences of actions, and managing working memory, it is not surprising that frontal dysfunction would cause major abnormalities in thinking and behavior.



Description

Figure 14.9 Blood Flow in Normal and Schizophrenic Brains During Card Sorting Test.
The upper images in (a) are of the left and right hemispheres of a normal brain; the brain of an individual with schizophrenia is below. Red and yellow represent high levels of activation. Note especially the activity in the dorsolateral prefrontal cortex, indicated in (b).

Source: (a) From "Physiologic Dysfunction of Dorsolateral Prefrontal Cortex in Schizophrenia: I. Regional Cerebral Blood Flow Evidence," by D. R. Weinberger, K. F. Berman, and R. R. Zec, 1986, *Archives of General Psychiatry*, *43*, pp. 114–124.

Neural Connections and Synchrony

Recent attention has been shifting away from localized deficits and focusing instead on disrupted coordination of neural activity across brain areas. For example, in normal controls performing a working-memory task, activity in the hippocampal formation varies together with prefrontal activity, but this coordination is absent in people with schizophrenia (Meyer-Lindberg et al., 2005). Stimulating inhibitory neurons in the hippocampus can restore the synchronous activity of information flowing through it (Marissal et al., 2018). Inadequate coordination between brain areas is at least partly due to white matter reduction; white matter loss has been consistently reported in the brains of people with schizophrenia, particularly in prefrontal and temporal areas (Begré & Koenig, 2008; Ellison-Wright & Bullmore, 2009). Diffusion tensor imaging shows that the quality of connections is compromised throughout much of the brain (B. R. Lee et al., 2013). Recent studies also documented an overall decrease in cortical thickness, changes in neuronal maturation, and reduced cortical folding in the cingulate-frontal-temporal circuit, suggesting that hypofrontality may be a result of decreased gray and white matter in frontal-associated circuits (Alexander-Bloch et al., 2014; Nanda et al., 2014).

Brain functioning is coordinated by synchronized firing that links the activity of neurons within a cortical area, across areas, and even between hemispheres. This synchronization is widely believed to be critical to perceptual binding and cognitive performance, and it is one of the functions disrupted in schizophrenia (Uhlhaas & Singer, 2010). Synchronized activity in frontal-thalamocortical circuits occurred at lower frequencies in patients (Ferrarelli et al., 2012), perhaps because the reduced

white matter connections cannot support coordination at higher frequencies. Frequency reduction averaged 10 Hz in the frontal cortex; the deficit was greatest in the prefrontal area, and the frequency loss there was correlated with positive and negative symptoms. To some extent, we can correlate the patterns of synchrony with the symptoms of schizophrenia; in patients with positive symptoms, for example, oscillation synchrony is enhanced within limited areas but is deficient between areas (Uhlhaas & Singer, 2010). This enhanced synchrony, which indicates hyperexcitability, is seen in the occipital area in visual hallucinators (Spencer et al., 2004) and in the left auditory cortex in auditory hallucinators (Spencer, Niznikiewicz, Nestor, Shenton, & McCarley, 2009). At the same time, auditory hallucinators fail to show normal synchrony between frontal and temporal areas while talking (Ford, Mathalon, Whitfield, Faustman, & Roth, 2002).

It may surprise you to learn that hallucinations are associated with activity in the respective sensory areas. Scans of the brains of people with schizophrenia show that language areas are active during auditory hallucinations and that visual areas are active during visual hallucinations (Figure 14.10; McGuire, Shah, & Murray, 1993; McGuire et al., 1995; Silbersweig et al., 1995). Because these areas are activated in normal individuals when they are engaged in “inner speech” (talking to oneself) and imagining visual scenes, it appears that the hallucinating person with schizophrenia is not simply imagining voices and images but is misperceiving self-generated thoughts.

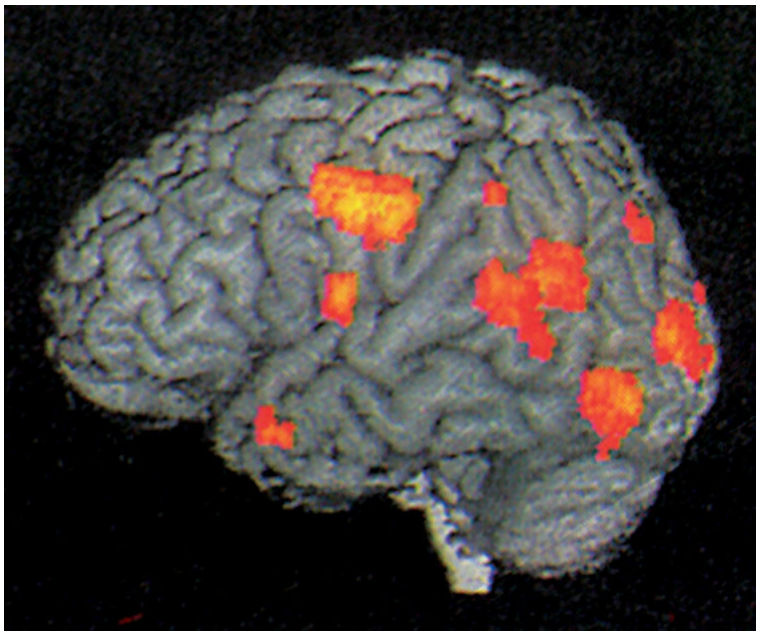
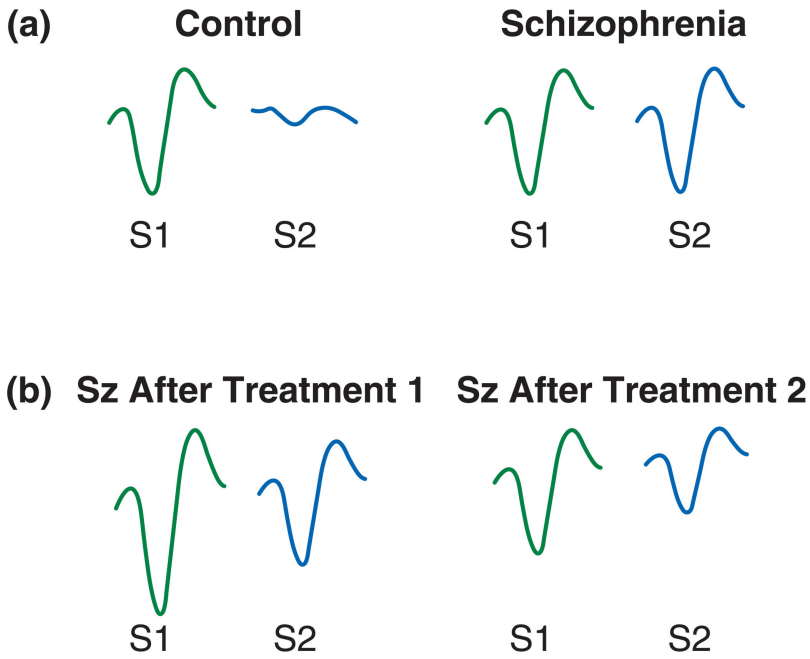


Figure 14.10 Brain Activation During Visual and Auditory Hallucinations in a Patient With Schizophrenia.

Source: From “A Functional Neuroanatomy of Hallucinations in Schizophrenia,” by D. A. Silbersweig et al., *Nature, 378,* pp. 176–179. Reprinted by permission of Nature, copyright 1995.

One of the most documented symptoms of schizophrenia is the inability to suppress environmental sounds. With *sensory gating* impaired, the intrusion of non-attended stimuli, such as traffic noise or a conversation in the next room, is not just annoying but can be interpreted as threatening. Impaired sensory gating can be a useful diagnostic tool for schizophrenia. Most people will “gate out” the second of two clicks presented a half-second apart, indicated by a reduction in the P50 EEG wave, but individuals with schizophrenia typically have an abnormally high P50 wave (Figure 14.11). This problem is also associated with reduced synchrony across wide areas of the brain (M. H. Hall, Taylor, Salisbury, & Levy, 2010). Atypical antipsychotics improve gating, and nicotine normalizes it (Adler et al., 2004; Kumari & Postma, 2005). The smoking rate declined in the United States from 42% in 1965 to about 15% in 2015

(Centers for Disease Control and Prevention, 2015b), but the rate remained about 80% among people with schizophrenia (Keltner & Grant, 2006), in an apparent attempt at self-medication. Besides sensory gating, nicotine improves several negative symptoms, including impaired visual tracking of moving objects, working memory, and other cognitive abilities (Sacco et al., 2005; Tregellas, Tanabe, Martin, & Freedman, 2005). Nicotine also appears to compensate for diminished functioning of nicotinic acetylcholine receptors (Deutsch et al., 2005), increase glutamate and GABA release, and increase dopamine levels in the prefrontal cortex where it is depleted in hypofrontality (Kumari & Postma, 2005; Sata et al., 2008). Three studies have linked schizophrenia with one of the genes responsible for nicotinic receptors (Deutsch et al., 2005; V. De Luca, Wang, et al., 2004).



Description

Figure 14.11 Absence of P50 Gating in Schizophrenia.
Two clicks are presented 500 milliseconds apart; healthy control participants show a reduced P50 EEG wave to the second click, a sign of gating (a, left), but those with schizophrenia do not (a, right). Gating is improved by some antipsychotics, either by increasing S1 or decreasing S2 (b).

Source: Figure 1 from "Translational utility of rodent hippocampal auditory gating in schizophrenia research: a review and evaluation," by J Smucny, K. E. Stevens, A. Olincy, & J. R. Tregellas, 2015, Translational Psychiatry, 5, pp. e587. Licensed under CC BY 4.0.

There may very well be other changes to the brain due to schizophrenia. A large coalition of European researchers and pharmaceutical companies is undertaking a €16.5 million ($18.8 million) study called PRISM (Psychiatric Ratings Using Intermediate Stratified Markers); they will follow individuals with schizophrenia and other neurological disorders to determine the biological roots of the negative symptom of social withdrawal that is common to the groups (Cuthbert, 2019).

Environmental Origins of the Brain and Transmitter Anomalies

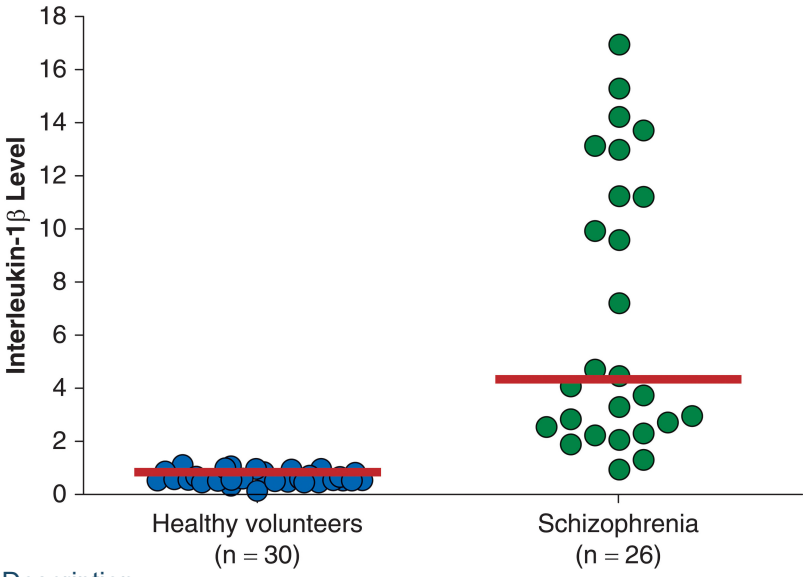
An obvious potential cause of brain defects would be head injury. Several studies have reported an association between schizophrenia and brain damage that occurred within a few years prior to diagnosis (reviewed in David & Prince, 2005; Leask, 2004). However, the studies have been criticized for methodological inadequacies, including reliance on patients' and relatives' memory of the injuries, casual diagnosis of

schizophrenia, and failure to consider accident proneness and preinjury symptoms as confounding factors (David & Prince, 2005; Nielsen, Mortensen, O'Callaghan, Mors, & Ewald, 2002). A later study of almost 114,000 Danish citizens found a strong correlation between severe head injury and schizophrenia; injury occurring between 11 and 14 years of age increased the likelihood of schizophrenia by 65% (Orlovska et al., 2014). However, researchers cannot separate the effects of the physical injury to the brain from the emotional effects of the stress and anxiety caused by the injury experience.

The evidence is stronger for a variety of influences at the time of birth or during the prenatal period. These include both physical complications (Cannon, Jones, & Murray, 2002) and emotional stresses on the mother, such as death of the father (Huttunen, 1989) and military invasion (van Os & Selten, 1998). Prenatal stress in mice results in upregulation of 5-HT_{2A} receptors and downregulation of glutamate receptors, both of which are seen in the brains of schizophrenia patients (Holloway et al., 2013). One indication that birth and pregnancy complications contribute to brain deficits is that they are associated with enlarged ventricles later in life (Pearlson et al., 1989). They are a possible explanation for the difference in ventricle size between identical twins (Bracha, Torrey, Gottesman, Bigelow, & Cunniff, 1992).

It is easy to see how birth complications, such as being born with the umbilical cord around the neck, could differentiate between twins, but different experiences in the womb require some explanation. Identical twins may share the same placenta and amniotic sac, or they may have their own, depending on whether the developing organism splits in two before or after the fourth day of development. Identical twins who did not share a placenta had an 11% concordance rate for schizophrenia, compared with 60% for those who shared a placenta, presumably due to the sharing of infections (J. O. Davis, Phelps, & Bracha, 1995). In spite of the importance of prenatal factors, some researchers believe that they produce schizophrenia only in individuals who are already genetically vulnerable (Schulsinger et al., 1984).

The **winter birth effect** refers to the fact that more people who develop schizophrenia are born during the winter and spring than during any other time of the year. The effect has been replicated in a large number of studies, some with more than 50,000 patients with schizophrenia as subjects (T. N. Bradbury & Miller, 1985). The important factor in winter births is not cold weather but the fact that infants born between January and May would have been in the second trimester of prenatal development in the fall or early winter, when there is a high incidence of infectious diseases (C. G. Watson, Kucala, Tilleskjor, & Jacobs, 1984). There is good evidence that the mother's exposure to *viral infections* during the fourth through sixth months of pregnancy (second trimester) increases the risk of schizophrenia. This appears to be caused not by the virus itself but by the immune reaction that it triggers. This conclusion is supported by a markedly higher level of interleukin-1β in the spinal fluid of first-episode patients, indicating that an immune response has occurred (Figure 14.12; Söderlund et al., 2009). Because the patients were infection free at the time, the infection must have occurred earlier, possibly during the prenatal period.

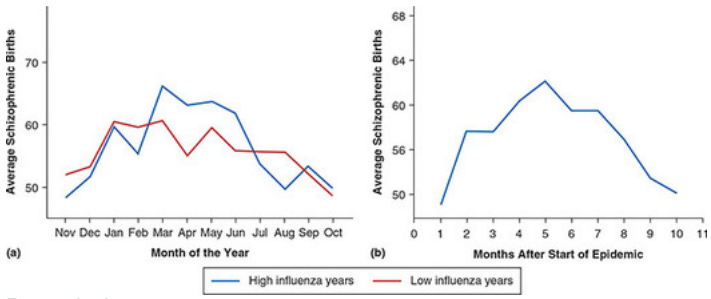


Description

Figure 14.12 Interleukin-1β Levels in Schizophrenia Patients and Controls. Elevated levels of this protein at the time of a first schizophrenic episode indicated that strong immune reactions had occurred in the past. Line indicates average level of Interleukin-1β.

Source: Adapted from "Activation of Brain Interleukin-1β in Schizophrenia," by J. Söderlund et al., 2009, *Molecular Psychiatry, 14,* pp. 1069–1071. Copyright © 2009 Nature Publishing Group. Used with permission.

Several illnesses have been implicated, but the effect of influenza has been researched most frequently, and a higher incidence of schizophrenic births has been confirmed following influenza outbreaks in several countries. Figure 14.13 shows that during years of high influenza infection, the birth rate of people later diagnosed with schizophrenia increases during winter and spring; also, there is a peak of such births a few months after the start of epidemics. However, these studies could not confirm that the individual mothers had been exposed to the influenza virus; by analyzing the blood specimens drawn from expectant mothers, Alan Brown and his colleagues (2004) found a seven-fold increased risk for schizophrenia and spectrum disorders when influenza antibodies were present, and they estimated that influenza infection accounts for 14% of schizophrenia cases. As was the case with stress, maternal infection with the influenza virus upregulates 5-HT_{2A} receptors and downregulates $mGlu_2$ receptors in the frontal cortex of the offspring (Moreno et al., 2011). Injecting pregnant mice with a drug that activates the immune system produced the same result, suggesting that immune responses are responsible for the receptor alterations in schizophrenia (Holloway et al., 2013).



Description

Figure 14.13 Relationship of Schizophrenic Births to Season and Influenza Epidemics in England and Wales (1939–1960).
(a) Schizophrenic birth rates by month during years of high and low influenza incidence. (b) Schizophrenic birth rate as a function of time from beginning of epidemic.

Source: From "Schizophrenia Following Pre-natal Exposure to Influenza Epidemics Between 1939 and 1960," by P. C. Sham et al., *British Journal of Psychiatry, 160,* pp. 461–466. Copyright 1992.

Prenatal starvation is another pathway to schizophrenia that until recently was the subject of controversy. The idea came about after the rate of schizophrenia doubled among the offspring of mothers who were pregnant during Hitler's 1944–1945 food blockade of the Netherlands (Susser et al., 1996). However, the interpretation was questionable because the sample was small and because toxins in the tulip bulbs the women ate to survive could have been to blame. But now data from a much larger sample of adults born during the 1959–1961 famine in China have confirmed the association, with an increase in schizophrenia from 0.84% to 2.15% (St. Clair et al., 2005).

Most of the environmental influences we have been discussing occur during pregnancy or birth; one, however, relates to the father. There is a greater risk of schizophrenia if the father's age at the time of conception exceeds 25, and by paternal age of 45, the risk has increased by 50% (Sörensen et al., 2014). The mechanism for this effect is unknown, but chances are it is epigenetic, due either to the normal aging process or to an accumulation of external environmental insults. Epigenetic effects in general can be traced to a variety of environmental influences, including toxins, diet, starvation, drugs, and stress; they likely account for most of the environmental influences we have been talking about. The fact that obesity in the Dutch hunger winter offspring was linked to epigenetic changes (see Chapter 6) makes us suspect the same mechanism in the cases of schizophrenia in that group. This is a relatively new area of investigation, so there has been little documentation of epigenetic influences in schizophrenia.

Schizophrenia as a Developmental Disease

Another hypothesis for the origin of schizophrenia is the neurodevelopmental hypothesis (Murray & Lewis, 1987). Defects in the brains of people diagnosed with schizophrenia apparently occur early in life, some at the time of birth or before. In some cases, it appears that many neurons in the temporal and frontal lobes failed to migrate to the outer areas of the cortex during the second trimester; they are disorganized and mislocated in the deeper white layers (Figure 14.14; Akbarian, Bunney, et al., 1993; Akbarian, Viñuela, et al., 1993). The hippocampus and prefrontal cortex are 30% to 50% deficient in reelin, a protein that functions as a stop factor for migrating neurons (Fatemi, Earle, & McMenomy, 2000; Guidotti et al., 2000). In addition, neurons generated from stem cells derived from skin cells of individuals with schizophrenia exhibited impairment of signaling molecules that are responsible for neuronal differentiation (Topol et al., 2016). These observations and the association of schizophrenia with birth trauma and prenatal viral infection all argue for early damage to the brain *or* a disruption of development.

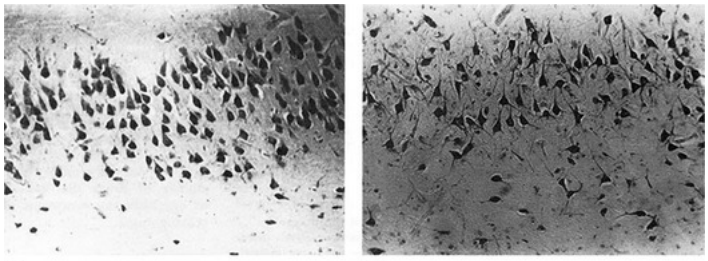


Figure 14.14 Neural Disorganization in Schizophrenia.
The neurons in the normal hippocampus have an orderly arrangement (a), but in the brain of an individual with schizophrenia, you can see that they have migrated in a haphazard fashion (b).

Source: Kovelman, J. A., & Scheibel, A. B. (1984). Courtesy of Arne Scheibel, UCLA.

This view is supported by behavioral data. Home movies of children who later developed schizophrenia revealed more negative facial expressions and physical awkwardness than in their healthy siblings; the movies were rated by judges who were unaware of the children's later outcome (E. F. Walker, Lewine, & Neumann, 1996). Among New Zealanders followed from age 3 to 32, those who later developed schizophrenia had deficits in learning, attention, and problem solving during childhood, and for each year of life, they fell an additional 2 to 3 months further behind other children (Reichenberg et al., 2010).

Gray matter deficit and ventricular enlargement are ordinarily present at the time of patients' diagnosis (Degreef et al., 1992). Most of the evidence indicates that the loss of brain volume occurs rapidly and dramatically in adolescence or young adulthood and then levels off (B. T. Woods, 1998). Adolescence is a particularly significant period in the development of schizophrenia. This is a time when symptoms often begin to develop and a time of brain maturation, including frontal myelination and connection of temporal limbic areas (Weinberger & Lipska, 1995). Thompson, Vidal, and colleagues (2001) identified a group of adolescents who had been diagnosed with schizophrenia and used MRIs to track their brain development. At the age of 13, there was little departure from the normal amount of gray matter loss that occurs with circuit pruning, but over the next 5 years, loss occurred in some areas as rapidly as 5% per year (Figure 14.15). The nature of the symptoms varied as the loss progressed from parietal to temporal to frontal areas. Studies have found no evidence of dying neurons or of the inflammation that would be expected with an ongoing degenerative disease; instead, gray matter deficits have been attributed to loss of synapses (Jarskog, Glantz, Gilmore, & Lieberman, 2005; D. A. Lewis & Levitt, 2002). This severe pruning may reflect the elimination of circuits that have already been weakened (D. A. Lewis & Levitt, 2002) by a lack of glutamate activity (Coyle, 2006) or through neuronal cell death pathways (Jarskog et al., 2005); this view is supported by the fact that the diagnosis of schizophrenia preceded significant gray matter reductions in the adolescents with schizophrenia.

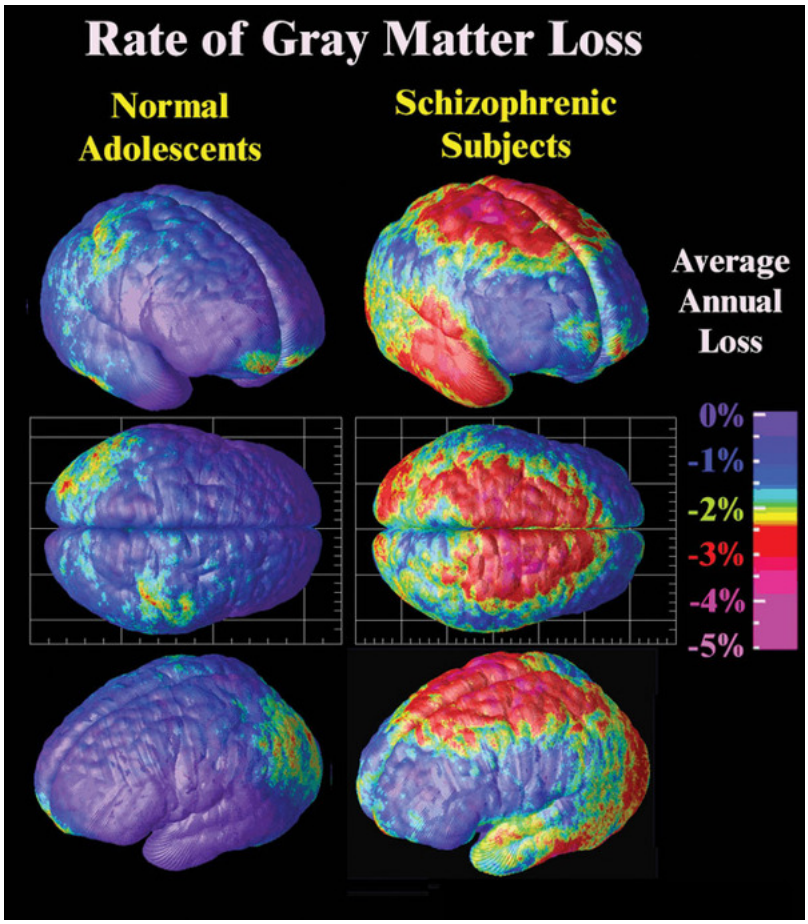


Figure 14.15 Gray Matter Loss in Adolescents With Schizophrenia.
There is some loss in the brains of normal adolescents due to circuit pruning, but the rate of loss is much greater in adolescents with schizophrenia. Red and pink areas represent 3% to 5% losses annually.

Source: From "Mapping Adolescent Brain Change Reveals Dynamic Wave of Accelerated Gray Matter Loss in Very Early-Onset Schizophrenia," by P. M. Thompson, *PNAS, 98,* pp. 11650–11655, fig. 1A, p. 11651, and fig. 5, p. 11653. © 2001 National Academy of Sciences, U.S.A. Used with permission.

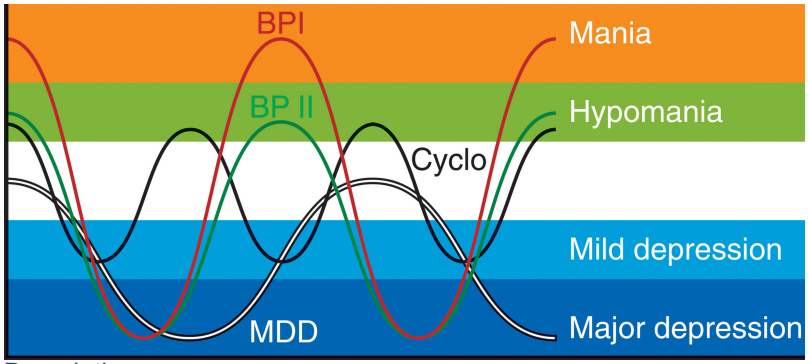
Concept Check

Take a Minute to Check Your Knowledge and Understanding

- What is the interplay between heredity and environment in schizophrenia?
- Describe the two symptom categories of schizophrenia.
- How are dopamine irregularities and brain deficits proposed to interact?
- What role does glutamate play in schizophrenia?

AFFECTIVE DISORDERS

The affective (mood) disorders include *depressive disorders*, *mania*, and *bipolar disorders* (Figure 14.16). Almost all of us occasionally experience **depression**, an intense feeling of sadness; we feel depressed over grades, a bad relationship, or loss of a loved one. This *reactive* depression can be severe, but major depression goes beyond the normal reaction to life's challenges. In **major depressive disorder (MDD)**, or unipolar depression, a person often feels sad to the point of hopelessness for weeks at a time; loses the ability to enjoy life, relationships, and sex; and experiences loss of energy and appetite, slowness of thought, and sleep disturbance. In some cases, the person is also agitated or restless. Stress is often a contributing factor, but MDD can occur for no apparent reason.



Description

Figure 14.16 Major Categories of Affective Disorders.
Individuals with BP I alternate between mania and major depression, those with BP II alternate between milder hypomania and major depression, those with cyclothymic disorder switch rapidly between hypomania and mild depression, and those with MDD alternate between normal mood and major depression. (BP I = bipolar I disorder; BP II = bipolar II disorder; cyclo = cyclothymic disorder; MDD = major depressive disorder.)

Mania involves excess energy and confidence that often leads to grandiose schemes. The *DSM*-5 classifies an individual with the disorder when three or more of the following symptoms are present: inflated self-esteem, decreased sleep, increased talkative nature, racing thoughts or ideas, easily distracted by unimportant stimuli, increase in goal-directed activities or agitation, and excessive involvement in activities that can have bad outcomes, such as overspending or sexual promiscuity (American Psychiatric Association, 2013). In addition, the disorder must be debilitating to the individual and can't be due to the effects of drugs. Kraepelin (1921) referred to mania as "increased busyness." Mania can occur on its own, which is rare, or it can alternate with periods of depression, which is called bipolar disorder.

? What are the affective disorders?

Bipolar disorder is a mix of both depression and mania. The *DSM*-5 considers bipolar disorder to be a cluster of disorders, separate from depressive disorders and serving as a bridge between depression and schizophrenia (American Psychiatric Association, 2013). Bipolar disorder was once called "manic-depressive" disorder, but as you will learn in this chapter, mania is not always a characteristic of this group of disorders. In **bipolar disorder**, a person alternates between periods of depression and either full-blown mania (bipolar I) or hypomania (agitation, anxiety; bipolar II). In addition, bipolar I patients often demonstrate psychotic features such as delusions, hallucinations, paranoia, or bizarre behavior, which has led psychologists to consider bipolar I as a bridge disorder between schizophrenia and depression. Finally, there is a third major category of bipolar disorder called cyclothymic disorder, in which individuals cycle rapidly between hypomania and mild depression. Two quotes provide some insight into the disorders from the patients' own perspectives (National Institute of Mental Health, 1986):

Depression: I doubt completely my ability to do anything well. It seems as though my mind has slowed down and burned out to the point of being virtually useless…. [I am] haunt[ed] … with the total, the desperate hopelessness of it all…. If I can't feel, move, think, or care, then what on earth is the point?

Mania: At first when I'm high, it's tremendous … ideas are fast … like shooting stars you follow until brighter ones appear … all shyness disappears, the right words and gestures are suddenly there…. Sensuality is pervasive, the desire to seduce and be seduced is irresistible. Your marrow is infused with unbelievable feelings of ease, power, well-being, omnipotence, euphoria … you can do anything … but, somewhere this changes.

The most recent data indicate that 3 out of 10 people will suffer a mood disorder in their lifetimes, most likely depression (R. C. Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). Women are two to three times more likely than men to suffer from MDD during their lifetimes; bipolar disorder occurs equally often in both sexes (Gershon, Bunney, Leckman, Van Eerdewegh, & DeBauche, 1976; P. W. Gold, Goodwin, & Chrousos, 1988) at a rate of about 4.5% (R. C. Kessler, Merikangas, & Wang, 2007). The risk for MDD increases with age in men, whereas women experience their peak risk between the ages of 35 and 45; the period of greatest risk for bipolar disorder is in the early 20s to around the age of 30.

Getting a handle on the economic burden of these disorders is difficult, because it depends on what costs are included and what assumptions are made. The annual cost for all mood disorders in the United States may reach $250 billion: $151 billion for bipolar disorders (Dilsaver, 2011) and $97.3 billion for MDD (Eaton et al., 2008). Regardless of the economic cost, depression is the third-largest cause of disability in women worldwide and fifth in men (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018).

Heredity

As with schizophrenia, there is strong evidence that affective disorders are partially heritable. Part of that evidence is the increased incidence of affective disorders among patients' relatives; for example, children of parents with depression are two to three times more likely to develop depression themselves (Sullivan, Neale, & Kendler, 2000). When one identical twin has an affective disorder, the probability that the other twin will have the illness as well is about 69%, compared with 13% in fraternal twins (Gershon et al., 1976). Lack of complete concordance in identical twins indicates that there is an environmental contribution. However, the concordance rate drops surprisingly little when identical twins are reared apart (J. Price, 1968), which may mean that the most important environmental influences occur in the prenatal period or shortly after. According to a meta-analysis of twin studies, the heritability for depression is 37% (Sullivan et al., 2000). Heritability is higher in women than in men (42% versus 29%; Kendler, Gatz, Gardner, & Pedersen, 2006), and women are twice as likely as men to develop depression (Kuehner, 2017).

In the past, identifying genes associated with psychological disorders required geneticists to start out with a suspected gene. A candidate gene might be chosen because it has a role in, for example, neural development or one of the neurotransmitter systems believed to be involved in the disorder. More than 100 candidate genes have been investigated by depression researchers, but the studies have yielded mixed results for a variety of reasons, including inadequately sized samples (Shadrina, Bondarenko, & Slominsky, 2018). Of the half-dozen best-documented genes identified this way, three have roles in dopamine and serotonin functioning. More recent technological advances have enabled researchers to scan the entire genome quickly and inexpensively. These genome-wide association studies

(GWAS) allow the researcher to compare stretches of DNA in people with the disorder and controls with no need for hypotheses about which genes might be related to the disorder. But doing a million or more statistical comparisons means that several genes will be identified by chance alone; the stringent correction for multiple comparisons that this requires makes it even harder to find genes that have a small effect. As a result, sample sizes numbering around 10,000 are required, and even with very large samples, very few new gene associations have emerged.

Like schizophrenia, depression is a very heterogeneous disorder, so one proposal for increasing the sensitivity of genetic studies is to examine subgroups separately. We've already seen that men and women differ in heritability, and a study found seven depression-related genes that were exclusive to men, nine that were exclusive to women, and only three that were shared between men and women (Zubenko, Hughes, Stiffler, Zubenko, & Kaplan, 2002). In other research, a genetic link on chromosome 3 was identified only when researchers limited their search to patients with severe depression (Breen et al., 2011). Stress history may also define genetically distinct groups. The most prominent environmental antecedents of depression involve stress: poverty, negative family relations, parental divorce, child maltreatment, and general stressful life events. Studies suggest that childhood abuse leads to a depression with a different onset, course, and response to treatment (Dunn et al., 2015). Some studies have indicated that the so-called short allele of the 5-HTTLPR segment of the serotonin transporter gene (*SLC6A4*) contributes to depression in individuals exposed to high levels of stress. But other results have been negative, and even meta-analyses disagree (Culverhouse et al., 2018; Oo, Aung, Jenkins, & Win, 2016). One reason may be that *FKBP5* and *CHRH1*, two genes that regulate the HPA axis, moderate the effects of childhood and later stress on adult depression (reviewed in Dunn et al., 2015). This points to the need to consider not only gene–environment interactions but gene–gene interactions.

A common characteristic of depression is disruption of the circadian (day–night) cycle, which is controlled by numerous genes (B. G. Bunney et al., 2015). At last count, at least 11 circadian genes were disrupted in patients with major depression (J. Z. Li et al., 2013). These genes are expressed in the pineal gland (which secretes the sleep-inducing hormone melatonin), the pituitary gland (which controls hormone levels in the body), and most importantly the anterior cingulate cortex (which, as we discussed in Chapter 8, is involved in autonomic functions, reward, decision making, and emotion). It is this last area that probably causes the alteration in mood we see in affective disorders.

Despite similarities between depression and bipolar disorder, they appear to be genetically independent of each other (P. W. Gold et al., 1988; Moldin, Reich, & Rice, 1991). In fact, there is a much higher genetic correlation between bipolar disorder and schizophrenia (68%) than mood disorders (43%; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Bipolar disorder is more heritable than either depression or schizophrenia, with estimates of 85% and 93% (Kieseppä, Partonen, Haukka, Kaprio, & Lönnqvist, 2004; McGuffin et al., 2003). Few genes have been confirmed, however, apparently again because of small sample sizes. A genome-wide study that included 9,747 patients confirmed three previously discovered genes and added two more (Mühleisen et al., 2014). The genes' functions involve neuronal calcium channels and cellular functioning and signaling. The Cross-Disorder Group study, with 33,332 patients, reported that some genes are shared among five disorders: bipolar disorder, major depressive disorder, schizophrenia, autism spectrum disorder, and attention-deficit/hyperactivity disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Genetic sharing is one of the arguments for considering these disorders as a continuum. Whether that is appropriate or not, you should understand that all five of these disorders do have a variety of functional and structural characteristics in common. Finally, mutations have been found in bipolar patients in three genes that control circadian rhythms, none of which overlapped with the five associated with depression (C. L. McGrath et al., 2009; Soria et al., 2010).

The Monoamine Hypothesis of Depression

The first effective treatment for depression was discovered accidentally, and theory again followed practice, rather than the other way around. *Iproniazid* was introduced as a treatment for tuberculosis, but it was soon discovered that the drug produced elevation of mood (Crane, 1957) and was effective as an antidepressant (Schildkraut, 1965). Iproniazid was later abandoned because of its side effects, but its ability to increase activity at the monoamine receptors led researchers to the **monoamine hypothesis** : that depression involves reduced activity at norepinephrine and serotonin synapses. You may remember that the monoamines also include dopamine, but because dopamine agonists such as amphetamines produced inconsistent therapeutic results, researchers have limited their interest to norepinephrine and serotonin.

? What is the monoamine hypothesis?

All the effective antidepressant drugs increase the activity of norepinephrine or serotonin, or both, at the synapses. They do this in different ways. Some block the destruction of excess monoamines by enzymes in the terminals (*monoamine oxidase inhibitors or MAOIs*), whereas others block reuptake at the synapse (*tricyclic antidepressants*). *Atypical (second-generation)* antidepressants affect a single neurotransmitter; for example, Prozac (fluoxetine) is one of several *selective serotonin reuptake inhibitors (SSRIs)*. Finally, some antidepressants have a mixed effect on multiple neurotransmitter systems and are effective for specific combinations of disorders. For instance, Cymbalta (duloxetine) is one of several *serotonin and norepinephrine reuptake inhibitors (SNRIs)*. This last group's effectiveness truly supports the monoamine hypothesis. The synaptic effects of antidepressants can occur within hours, but symptom improvement usually takes 2 to 3 weeks through the gradual modification of abnormal cortical circuits.

Additional evidence to support the monoamine hypothesis is that serotonin and norepinephrine are involved in behaviors that are disturbed in affective disorders. Serotonin plays a role in mood, activity level, sleep and daily rhythms, feeding behavior, sexual activity, body temperature regulation, and cognitive function (Meltzer, 1990; Siever et al., 1991). And because the noradrenergic system is involved in responsiveness and sensitivity to the environment, reduced norepinephrine activity may contribute to the depressed individual's slowed behavior, lack of goal-directed activity, and unresponsiveness to environmental change (Siever et al., 1991).

Earlier, we saw that nicotine provides some relief from symptoms of schizophrenia. Non-nicotine ingredients in tobacco smoke also have been found to act as monoamine oxidase inhibitors. This would explain why smoking is so frequent among those with depression and why they have difficulty giving up smoking (J. S. Fowler et al., 1996; Khalil, Davies, & Castagnoli, 2006). We mention a therapeutic effect of smoking for the second time only to illustrate again how people may self-medicate without being aware they are doing it and why some people have so much trouble quitting; if it sounds as though the benefits of smoking outweigh the cost to the smoker's health, reread the section on nicotine in Chapter 5. Figure 14.17 is a dramatic demonstration of the extensive effect of smoking on monoamine oxidase levels throughout the body.

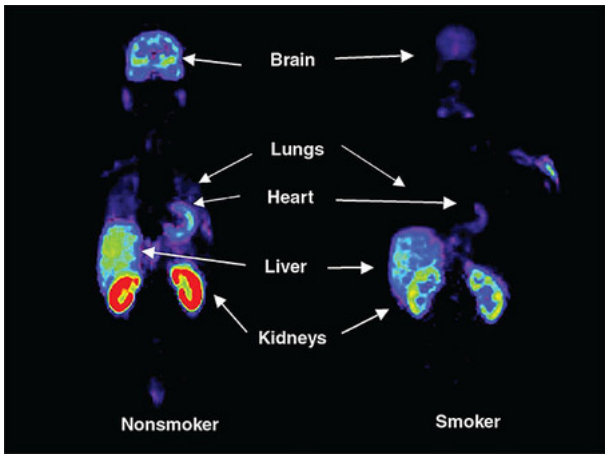


Figure 14.17 Monoamine Oxidase Levels in the Body of a Nonsmoker and a Smoker. PET scans were done using a radioactive tracer that binds to monoamine oxidase B. Levels were reduced 33% to 46% in smokers. Monoamine oxidase reduction can have beneficial, detrimental, or neutral effects, depending on the location and other conditions.

Source: From "Low Monoamine Oxidase B Levels in Peripheral Organs of Smokers," by J. S. Fowler et al., *PNAS, 100,* fig. 2, p. 11602. © 2003 National Academy of Sciences, U.S.A. Used with permission.

Treatment resistance and the delay required for drugs to take effect are serious issues, especially if the patient is suicidal. Experiments with ketamine, which was developed as an anesthetic but gained infamy as a club drug, suggest that these problems might be avoidable. Ketamine appears to work well in individuals who don't improve using other methods (Fava et al., 2018). In a study with patients who had shown resistance to at least two antidepressant drugs, a single injection of ketamine quickly alleviated depression in 68%, and the improvement lasted 7 days in 46% of the patients (Murrough et al., 2013). Relapse time is highly variable, though, and ketamine appears to be most valuable as a temporary treatment (aan het Rot et al., 2010). Ketamine also interests us because its effect is not on norepinephrine or serotonin; instead, it has its antidepressant effect by activating AMPA receptors (Zanos et al., 2016), implicating glutamate function in depression as well as in schizophrenia.

About 30% to 50% of depressed patients fail to respond to drug therapy, a statistic made worse by the realization that the placebo response rate alone is 30% (Depression Guideline Panel, 1993). Lack of response is partly related to symptom severity; patients with mild or moderate symptoms receive little or no relief, but for patients with severe depression, the benefit of medications is substantial (Fournier et al., 2010). So how do we treat drug-resistant forms of depression? Cognitive-behavioral therapy is generally about as effective as antidepressants, and when it was added to the usual treatment in resistant patients, depression scores improved by 50% or more in 46% of patients, compared with 22% in those who remained in typical treatment (Wiles et al., 2013). One thing that must be clear to you by now is how much therapeutic effectiveness depends on designing drugs to affect the right receptors and avoiding effects at sites that would produce side effects. This is the subject of A Further Look.

A Further Look:

Targeting Drugs to Specific Receptors

Source: iStockphoto.com/BCFC.

As we have already mentioned, the most prescribed class of antidepressant medications today is the SSRIs. Although mood disorders are most commonly linked to serotonin (5-HT), abnormal function of other receptors and neurotransmitters can cause similar behavioral changes. For instance, there could be an imbalance of norepinephrine or dopamine. Newer antidepressant medications are designed to stimulate different classes of receptors or to bind to only one of several receptor subtypes. For instance, a class of drugs called SNRIs increases the amounts of both serotonin and norepinephrine, which is useful for individuals with depression as well as emotional pain. Examples of these drugs include Cymbalta, Effexor, and Pristiq. Another class is the NDRIs, a relatively new class of drugs that raise norepinephrine as well as dopamine levels. These drugs are useful for treating some types of depression as well as attention-deficit/hyperactivity disorder (ADHD). Examples of this group include Focalin, Ritalin, Concerta, and Wellbutrin. One drug that targets a specific receptor subtype is the atypical antipsychotic Pimavanserin (in clinical trials), which specifically treats psychosis associated with Parkinson's disease by stimulating 5-HT_{2A} receptors and leaving the other serotonin receptor subtypes alone (Friedman, 2013). Another drug, Cariprazine, stimulates the D_2 receptor family and not the D_1 subfamily, which improves mania symptoms of both schizophrenia and bipolar I (Tohen, 2015). One of the oddest atypical antidepressants is Remeron (mirtazapine), which is classified as a norepinephrine and specific serotonergic antidepressant (NaSSA). This drug enhances the release of norepinephrine, increases serotonin release by presynaptic neurons, and modulates serotonin receptors in a complex way: It blocks 5-HT_2 and 5-HT_3 receptors so that the increased serotonin can bind only to 5-HT_1 receptors (Antilla & Leinonen, 2001). The 5-HT_2 and 5-HT_3 receptors are associated with anxiety, changes in appetite, sexual dysfunction, and memory problems, so targeting only the 5-HT_1 receptors provides effective antidepressant relief without as many side effects as with SSRIs (Schreiber, Melon, & DeVry, 1998).

As we just indicated, there are many types of each receptor in your nervous system. You have at least seven different serotonin receptor families, two dopamine receptor families, and at least five norepinephrine receptors (two alpha and three beta). Many of these receptors are found not only in the brain but also throughout the body, and stimulating them broadly using tricyclic antidepressants, MAOIs, or even SSRIs triggers most of the unpleasant side effects of those drugs. The future of psychopharmacology will therefore be in designer drugs that interact with only a subset of receptors that match an individual's symptoms and neurobiology.

Electroconvulsive Therapy

In extreme cases of treatment nonresponse or because of suicidal behaviors, an alternative is electroconvulsive therapy. **Electroconvulsive therapy (ECT)** involves applying 70 to 130 volts of electricity to the head of an anesthetized patient, which produces a seizure accompanied by convulsive contractions of the neck and limbs and lasting about a half-minute to a minute (Figure 14.18). Without the seizure activity in the brain that produces the convulsions, the treatment does not work. Within a few minutes, the patient is conscious and coherent, though perhaps a bit confused; the patient does not remember the experience. Usually ECT is administered two to three times per week for a total of 6 to 12 treatments.

Figure 14.18 A Patient Being Readied for Electroconvulsive Therapy.

David Cooper / Contributor / Getty Images

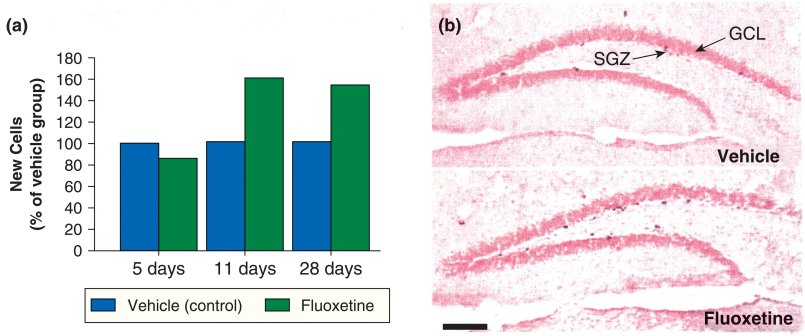
ECT is the most controversial of the psychiatric therapies. Producing convulsions by sending a jolt of electricity through the brain *sounds* inhumane, and, in fact, the procedures used in the early days of ECT treatment often resulted in bone fractures and long-term memory deficits. Now patients are anesthetized and given muscle relaxants that eliminate injury and reduce emotional stress. The numbers of treatments and the voltage have been reduced, and stimulation is delivered in brief pulses rather than continuously. Though bilateral electrode placement produces a faster response that is desirable with suicidal patients, unilateral right hemisphere ECT is usually favored because it minimizes cognitive side effects, such as temporary memory impairment, that can last for months (Crowe, 1984; Kellner, Tobias, & Wiegand, 2010; Weeks, Freeman, & Kendell, 1980). Later studies even demonstrated that cognitive performance improves over pretreatment levels as the depression lifts (Sackeim et al., 1993). Brain scans and autopsies of patients and actual cell counts in animal subjects show no evidence of brain damage following ECT (reviewed in Devanand, Dwork, Hutchinson, Bolwig, & Sackheim, 1994).

ECT is usually reserved for patients who do not respond to the medications or who cannot take them due to extreme side effects or because of pregnancy. In a recent meta-analysis, treatment-resistant patients receiving ECT were nine times more likely to show significant improvement than those receiving other forms of treatment (Mutz et al., 2019). ECT also works especially well when depression or mania is accompanied by psychosis (Depression Guideline Panel, 1993; Potter & Rudorfer, 1993), and it works rapidly, which is beneficial to suicidal patients who cannot wait for weeks while a drug takes effect (Rudorfer, Henry, & Sackeim, 1997). The disadvantage of ECT is that its benefit is often short term, but the patient can usually be maintained on drug therapy once a round of ECT has been completed.

ECT is effective with depression, mania, and schizophrenia, which suggests that its effects are complex, and research bears this out. Several changes occur at the brain's synapses. Like the drugs, ECT increases the sensitivity of postsynaptic serotonin receptors (Mann, Arango, & Underwood, 1990); in addition, the sensitivity of autoreceptors on the terminals of norepinephrine- and dopamine-releasing neurons is reduced, so the release of those transmitters is increased. A temporary slowing of the EEG, which is correlated with therapeutic effectiveness, suggests that ECT synchronizes neuronal firing over large areas of the brain (Ishihara & Sasa, 1999; Sackeim et al., 1996). This reduced excitability is likely due to the fact that ECT increases diminished GABA concentrations (Sanacora et al., 2003). However, as you will see in the next section, both antidepressants and ECT now appear to trigger dramatic remodeling of the depressed brain.

Antidepressants, ECT, and Neural Plasticity

Although antidepressant drugs and ECT have been used to treat depression for more than half a century, we are not sure how they work. Most puzzling is the delay between neurotransmitter changes and symptom relief; hypotheses that changes in receptor sensitivity account for the delay have not been successful (Yamada, Yamada, & Higuchi, 2005). A promising lead is that antidepressant drugs, lithium, and ECT all increase neuronal birth rate in the hippocampus, at least in rodents and presumably in humans as well (Figure 14.19; Inta et al., 2013; Mendez-David, Hen, Gardier, & David, 2013; Sairanen, Lucas, Ernfors, Castrén, & Castrén, 2005). Although increased neurogenesis can be detected within hours of antidepressant treatment, the time required for new hippocampal neurons to migrate to their new locations and form functional connections closely matches the delay in symptom improvement (Sairanen et al., 2005).



Description

Figure 14.19 Increased Neurogenesis in the Hippocampus During Antidepressant Treatment.
(a) Antidepressant treatment produced a 60% increase in neurogenesis, compared with administration of inert material (vehicle). (b) Brown dots are new cells (preneurons).

Source: From "Requirement of Hippocampal Neurogenesis of the Behavioral Effects of Antidepressants," by L. Santarelli et al., *Science*, *301*, 805–809, fig. 2a and 2b, p. 806. © 2003. Reprinted with permission from AAAS.

After new cell development was blocked by X radiation, antidepressants no longer had an effect in mice, suggesting that neurogenesis is required for antidepressant action (Santarelli et al., 2003). An increase in cell numbers is not the basis, however, because cell death also accelerates; some researchers have suggested that the therapeutic effect is due to the greater plasticity of new cells (Gould & Gross, 2002), a point we saw in Chapter 12 in relation to their lower threshold for LTP. However, when researchers used a drug instead of X radiation to block neurogenesis, antidepressant effect was not diminished (Bessa et al., 2009). All three of the antidepressant drugs used increased dendritic remodeling and synaptic contact; this led the researchers to

conclude that antidepressant drugs work by enhancing plasticity rather than by promoting neurogenesis.

Both antidepressants and ECT modify activity in a large number of genes, especially in the hippocampus; most of those genes contribute to neural plasticity and neuron survival, as well as to neurogenesis (Altar et al., 2004; Yamada et al., 2005). And a recent study demonstrated stronger and more stable connections between the hippocampus and emotional centers of the brain following ECT administration (Kubicki et al., 2018). Therefore, neurogenesis might contribute to antidepressant effect, but restoration of plasticity might be more important.

Rhythms and Affective Disorders

As we mentioned earlier, several circadian rhythm genes are implicated in depression, so it should be no surprise that depressed people often have problems with their biological rhythms. The **circadian rhythm** —the one that is a day in length —tends to be phase advanced in patients with affective disorders; this means that the person feels sleepy early in the evening and then wakes up in the early morning hours, regardless of the previous evening's bedtime (Dew et al., 1996). The person also enters rapid eye movement sleep earlier in the night and spends more time in this state than normal (Kupfer, 1976). As you will learn in Chapter 15, rapid eye movement (REM) sleep is the stage of sleep during which dreaming occurs; the excess REM sleep is at the expense of the other stages of sleep. Patients with MDD share this early onset of REM sleep with 70% of their relatives, and relatives with reduced REM latency are three times more likely to be depressed than relatives without reduced latency (Giles, Biggs, Rush, & Roffwarg, 1988).

? What are the roles of daily rhythms and seasons?

Circadian Rhythms and Antidepressant Therapy

Some patients who are unresponsive to antidepressant medication can get relief from their depression by readjusting their circadian rhythm. They can do this simply by staying up a half hour later each night until they reach the desired bedtime. In some patients, this treatment results in a relief from depression that lasts for months (D. A. Sack, Nurnberger, Rosenthal, Ashburn, & Wehr, 1985).

Some depressed patients also benefit temporarily from sleep deprivation (called "wake therapy"). This was initially seen with REM sleep deprivation, which is accomplished by waking the person every time the EEG indicates that sleep has moved into the REM stage (J. C. Wu & Bunney, 1990). Interestingly, most antidepressant drugs also suppress REM sleep (G. W. Vogel, Buffenstein, Minter, & Hennessey, 1990). Later research showed that depressed individuals also improve following non-REM sleep deprivation (Landsness, Goldstein, Peterson, Tononi, & Benca, 2011) or total overnight sleep deprivation (Giedke & Schwärzler, 2002). Several mechanisms have been proposed for the improvements in mood: Sleep deprivation increases serotonin and norepinephrine and modulates dopamine activity (Adrien, 2002; Hipolide et al., 2005; Mogilnicka, 1981). Sleep deprivation also modulates NMDA receptor activity, which may protect the brain against the neurodegeneration seen in individuals suffering from long-term affective disorders (Novati, Hulshof, Granic, & Meerlo, 2012).

Seasonal Affective Disorder

There is another rhythm that is important in affective disorders; some people's depression rises and falls with the seasons and is known as **seasonal affective disorder (SAD)**. This is on a **circannual rhythm**, one that follows the changes of the seasons. Approximately 10% to 20% of depressed individuals also suffer from SAD (Magnusson, 2000), and 71% of SAD patients are women (Faedda et al., 1993). Most SAD patients are more depressed during the fall and winter and then improve in the

spring and summer, which parallels onset for schizophrenia as well (Owens & McGorry, 2003). Shorter days and reduced daylight appear to be important in winter depression: The prevalence of SAD is five times higher in New Hampshire as in Florida (L. N. Rosen et al., 1990). Symptoms improve when a patient travels farther south (or north, if in the Southern Hemisphere) even for a few days, and some report increased depression during cloudy periods in the summer or when they move to a home or office with fewer windows. While depressed, they usually sleep excessively, and they often have increased appetites, especially for carbohydrates, and gain weight. Even in their "good season," things are not always good: Sufferers may experience a mild mania-like activation in non-SAD seasons. For a minority of individuals with SAD, they are more depressed in the summer and feel better during the winter (Wehr, Sack, & Rosenthal, 1987). Summer depression appears to be temperature related: Traveling to a cooler climate, spending time in an air-conditioned house, and taking several cold showers a day improves the symptoms. Although seasonal influences on affective disorder have been known for 2,000 years and documented since the mid-1850s, summer depression has received comparatively little attention, so we will restrict our discussion to winter depression.

A treatment for winter depression is **phototherapy** —having the patient sit in front of high-intensity lights for a couple of hours or more per day (Figure 14.20). Patients begin to respond after 2 to 4 days of treatment with light that approximates sunlight from a window on a clear spring day; they relapse in about the same amount of time following withdrawal of treatment (Rosenthal et al., 1985). The fact that midday phototherapy is effective suggests that the increased amount of light is more important than extending the length of the shortened winter day; the observation that suicide rate is related to a locale's *amount* of clear sunlight, rather than the number of hours of daylight, supports this conclusion (Wehr et al., 1986). Phototherapy resets the circadian rhythm (Lewy, Sack, Miller, & Hoban, 1987), so it is also helpful with circadian rhythm problems, including jet lag, delayed sleep syndrome, and difficulties associated with shift work (Blehar & Rosenthal, 1989).

Figure 14.20 A Woman Uses a High-Intensity Light to Treat Her Seasonal Affective Disorder.

Source: Science & Society Picture Library/SSPL/Getty Images.

Physiological mechanisms for disorders of circadian and circannual rhythms include both serotonin system and prefrontal cortex changes. PET scans taken during a winter episode of SAD showed higher levels of serotonin reuptake than during the summer, indicating that lowered serotonin activity is involved in winter depression (Figure 14.21; McMahon et al., 2016). Drugs that increase serotonin activity alleviate the depression and reduce carbohydrate craving (O'Rourke, Wurtman, Wurtman, Chebli, & Gleason, 1989). As we saw in Chapter 5, eating carbohydrates increases brain serotonin levels. So rather than thinking that SAD patients lack willpower when they binge on junk food and gain weight, it might be more accurate to think of them as self-medicating with carbohydrates. But what areas of the brain change seasonally? A recent study suggests that the dorsolateral prefrontal cortex contains genes activated on a seasonal basis (Lim et al., 2017).

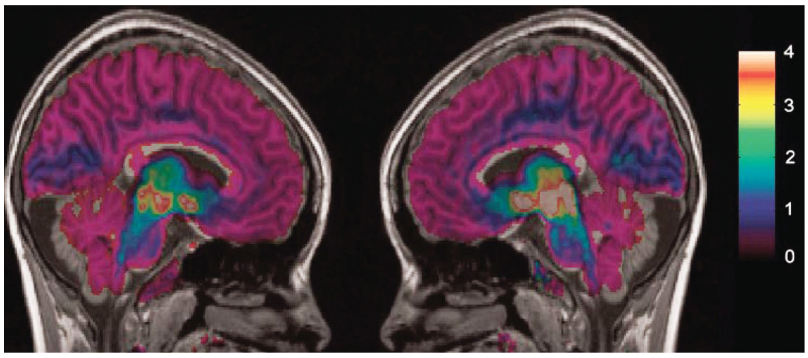


Figure 14.21 Serotonin Reuptake Is Abnormally High in SAD Patients.
PET scans of a 22-year-old woman during the summer (left) and during the winter with high levels of SAD (right). The amount of serotonin reuptake was much higher in the winter (increased red and white colors within the blue areas), indicating less available serotonin for modulating mood.

Source: From "Seasonal Difference in Brain Serotonin Transporter Binding Predicts Symptom Severity in Patients with Seasonal Affective Disorder," by B. McMahon et al., *Brain, 139,* 1605–1614, Fig. 2, p. 1611. © 2016. Reprinted with permission.

Bipolar Disorder and Related Disorders

The mystery of major depression is far from solved, but bipolar disorder is even more puzzling. Bipolar patients vary greatly in their symptoms: The depressive cycle usually lasts longer than mania, but either may predominate. There are three major forms of bipolar disorder: bipolar I (major depressive episodes with occasional manic episodes), bipolar II (major depression with mild hypomanic episodes), and cyclothymic disorder (frequent alternation between hypomanic and mild depressive episodes that are not severe enough for a diagnosis of bipolar II). Some patients cycle between depression and mania regularly (this is called *rapid cycling*), whereas others are unpredictable; cycles usually vary from weeks to months in duration, although some patients switch as frequently as every 48 hours (Bunney, Murphy, Goodwin, & Borge, 1972). Stress often precipitates the transition from depression into mania, followed by a more spontaneous change back to depression; the prospect of discharge from an inpatient facility is particularly stressful and often will precipitate the switch into mania. However, as bipolar disorder progresses, manic episodes tend to occur independently of life's stresses (P. W. Gold et al., 1988).

It appears that bipolar disorder involves increased sensitivity to dopamine and either decreased sensitivity to serotonin or a more general dysregulation in the dopaminergic system (Miklowitz & Johnson, 2006). Drugs used to treat the disorder include several second-generation antipsychotics, lithium, and the anticonvulsants carbamazepine and valproate. Anticonvulsants normally stabilize electrical activity in the brain and are typically used for treating epilepsy. **Lithium**, an element administered in the form of lithium carbonate, is the medication of choice for bipolar illness (Won & Kim, 2017); it is most effective in reducing the manic phase, but it also prevents further depressive episodes. Examination of lithium's effects has not identified any critical neurotransmitters, partly because lithium affects several transmitter systems, such as dopamine, NMDA, and GABA receptors (Worley, Heller, Snyder, & Baraban, 1988). It may be that lithium stabilizes these neurotransmitter and receptor systems to prevent the large activity swings seen in manic-depressive cycling; its dual role as an antidepressant argues for a normalizing effect rather than a directional one (Gitlin & Altshuler, 1997).

Closer examination, however, has revealed a specific effect on mania; lithium and valproate indirectly inhibit protein kinase C (PKC), a family of intracellular messengers that regulate neural excitability and a target for novel drugs for bipolar disorder (reviewed in DiazGranados & Zarate, 2008). The breast cancer drug tamoxifen is used to block estrogen receptors, but it also inhibits PKC. Tamoxifen,

both by itself and in combination with other drugs such as benzodiazepines (anti-anxiety drugs discussed in Chapter 5), has been shown to be effective in reducing manic symptoms in five studies (reviewed in Talaei et al., 2016). In a Phase 2 clinical trial, 90% of patients receiving tamoxifen with lithium were considered in remission, versus 55% receiving lithium alone (Amrollahi et al., 2011). Tamoxifen itself may not be practical as a treatment for bipolar disorder, because it is a selective estrogen receptor modulator (SERM) that antagonizes estrogen activity, which can be problematic in women at high doses; if the drug continues to prove effective, an alternative that targets PKC only will have to be found.

? What brain irregularities are involved in affective disorders?

Neurological Anomalies in Affective Disorders

As with schizophrenia, affective disorders are associated with structural abnormalities in several brain areas. Again, a larger ventricle size suggests loss of brain tissue, but the reductions are small and are not always found (Depue & Iacono, 1989). A review of numerous studies of depression reveals volume deficits in prefrontal areas, especially the dorsolateral cortex and the anterior cingulate cortex, as well as in the hippocampus (R. J. Davidson, Pizzagalli, Nitschke, & Putnam, 2002). Volume reduction apparently precedes depression rather than being a degenerative consequence of it; it is evident at the time of patients' first episode, and it can even be detected in the nondepressed offspring of patients (M. C. Chen, Hamilton, & Gotlib, 2010; Peterson et al., 2009; Zou et al., 2010). The amygdala is enlarged in depression (R. J. Davidson et al., 2002), and enlargement of the left hypothalamus is correlated with the severity of depression and anxiety in both MDD and bipolar disorder (Schindler et al., 2019). Enlargement of both of these structures apparently reflects the high levels of stress and HPA axis activation that characterize depression.

These structural alterations are accompanied by changes in activity level. Not surprisingly, total brain activity is reduced in MDD patients (Sackeim et al., 1990) and in bipolar patients when they are depressed (Baxter et al., 1989). Gray matter is particularly reduced in the hippocampus, the orbitofrontal cortex that regulates emotions (Figure 14.22; Egger et al., 2008), the basal forebrain (Ribiez et al., 2013), the prefrontal cortex, and the cingulate cortex (Arnone, McIntosh, Ebmeier, Munafò, & Anderson, 2012). In addition, there is lower activity in parts of the emotional regulation circuits in the brain that connect to the prefrontal lobe (Janiri et al., 2019). These decreases in brain tissue volume and activity have been postulated to be predictors not only for depression but also for the likelihood that the person will improve following antidepressant treatment (Ribiez et al.). What *is* surprising is that some areas are *more* active in depressed patients. Among these are brain areas responsible for attention and filtering information, which impairs decision making and judgment (Janiri et al.). In addition, blood flow is higher in the amygdala and a frontal area connected to the amygdala called the *ventral prefrontal cortex* (Figure 14.23). The ventral prefrontal area may also be a "depression switch," because activation comes and goes with bouts of depression. The amygdala continues to be active between episodes and returns to normal only after the remission of symptoms. Activity in the amygdala corresponds to the *trait* of depression—the continuing disorder—whereas activation of the ventral prefrontal area indicates the *state* of depression, which subsides from time to time in some individuals (Drevets, 2001; Drevets et al., 1992; Drevets & Raichle, 1995).

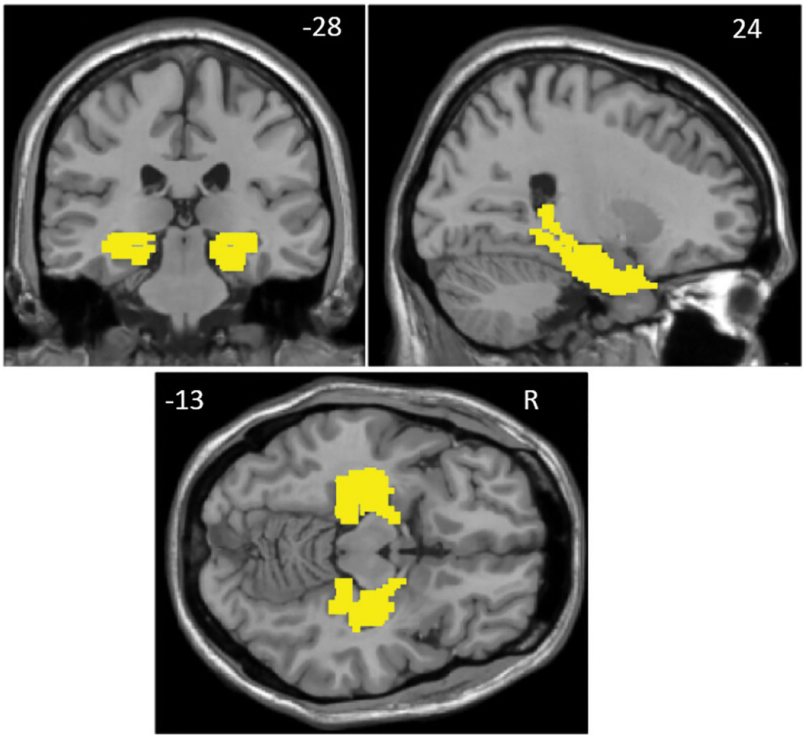


Figure 14.22 Reduction in Gray Matter in Elderly Depressed Patients.
Elderly patients with depression exhibited significant declines in gray matter in the amygdala (a), orbitofrontal cortex (b), and hippocampus (b, c). Yellow indicates severity of loss compared to elderly patients without depression.

From Zhou, H., Li, R., Ma, Z. et al. Smaller gray matter volume of hippocampus/parahippocampus in elderly people with subthreshold depression: a cross-sectional study. BMC Psychiatry 16, 219 (2016).

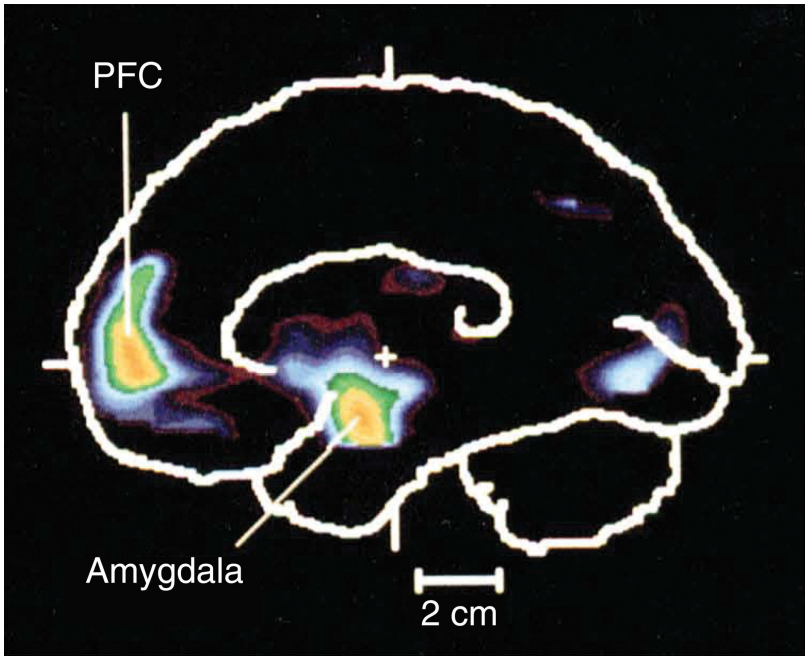


Figure 14.23 Increased Activity in the Ventral Prefrontal Cortex (PFC) and Amygdala in Depression.

Source: From “A Functional Anatomical Study of Unipolar Depression,” by W. C. Drevets et al., *Journal of Neuroscience, 12,* pp. 3628–3641. © 1992 Society for Neuroscience. Used with permission.

It is also not surprising that during a manic episode, brain metabolism increases from its depressed level by 4% to 36% (Figure 14.24; Baxter et al., 1989). The *subgenual prefrontal cortex* is particularly interesting because it has been suggested as a possible “switch” controlling bipolar cycling (Figure 14.25). Its metabolic activity is reduced during both MDD and bipolar depression but increases during manic episodes (Drevets et al., 1997). The structure is a part of the cingulate cortex, located at the midline; it is in a good position to act as a bipolar switch, because it has extensive connections to emotion centers, such as the amygdala and the lateral hypothalamus, and it helps regulate neurotransmitters involved in affective disorders. Several structural differences have been reported in bipolar disorder, but only a few have stood up to replication: decreased thickness and glial density in the anterior cingulate cortex, reduced density of neurons in parts of the amygdala, and decreases in a subset of neurons in the prefrontal cortex (Harrison, Colbourne, & Harrison, 2018).

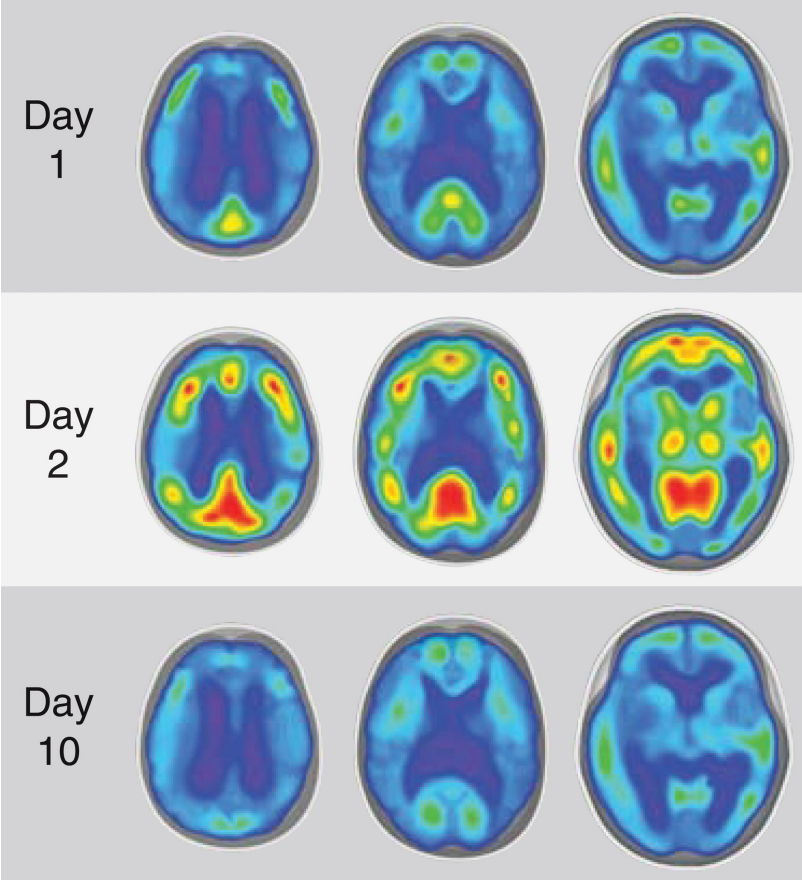
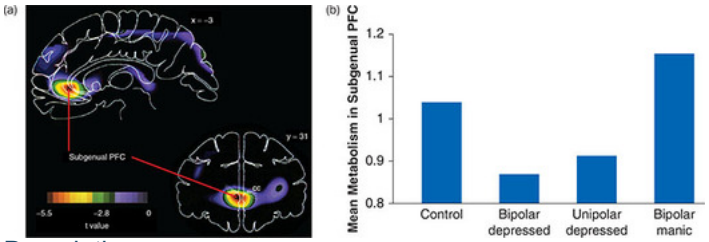


Figure 14.24 Glucose Metabolism Increase During Mania in a Rapid-Cycling Bipolar Patient.
The middle row shows the sudden increase in activity during a manic episode, just a day after the previous scan during depression. In the bottom row, the patient had returned to the depressed state.

Source: From “Cerebral Metabolic Rates for Glucose in Mood Disorders: Studies With Positron Emission Tomography and Fluorodeoxyglucose F18,” by L. R. Baxter et al., 1985, *Archives of General Psychiatry, 42,* pp. 441–447.



Description

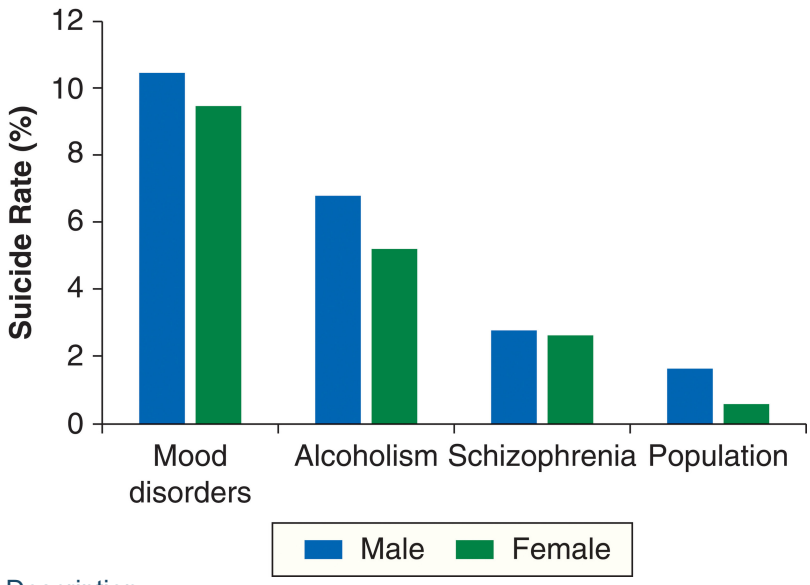
Figure 14.25 Activity in the Subgenual Prefrontal Cortex in Depression and Mania. (a) The dark areas in the subgenual prefrontal cortex indicate decreased activity during depression. (b) Comparison of groups shows that activity in the subgenual PFC is lower during depression and higher during mania, which suggests that it controls cycling between depression and mania.

Sources: (a) From "Subgenual Prefrontal Cortex Abnormalities in Mood Disorders," by W. C. Drevets et al., *Nature, 386,* 824–827. © 1997 Macmillan Publishing Inc. (b) From "Neuroimaging and Neuropathological Studies of Depression: Implications for the Cognitive-Emotional Features of Mood Disorders," by W. C. Drevets, *Current Opinion in Neurobiology, 11*, pp. 240–249, fig. 4b. © 2001 with kind permission of Elsevier.

Both MDD and bipolar patients have anomalies in functional brain connectivity. In depression, this takes the form of increased as well as decreased connectivity. Research has consistently reported decreased connectivity within the frontoparietal network but increased connectivity between the frontoparietal network and default mode network (DMN) and increased connectivity within the DMN (M. Yu et al., 2019). In bipolar disorder, connectivity is reduced in the cortex, corpus callosum, and thalamus (Barysheva, Jahanshad, Foland-Ross, Altshuler, & Thompson, 2013). These changes can be developmental in origin: Stress and trauma early in life can alter resting state brain networks, which increases the risk of developing depression later in life (M. Yu et al., 2019). Treatment can increase deficient connectivity between some areas (Heller et al., 2013) and decrease excess connectivity in others (Perrin et al., 2012). In both cases, the changes in connectivity were accompanied by symptom improvement.

Suicide

According to the World Health Organization (2014), more than 800,000 suicide deaths occur worldwide each year; twice as many men as women take their own lives, and suicide is the second leading cause of death among those ages 15 to 29. The suicide rate increased 31% between 2001 and 2017 in the United States, with males committing suicide four times as often as females (National Institute of Mental Health, 2019b). Ninety percent of people who attempt suicide have a diagnosable psychiatric illness; mood disorder alone accounts for 60% of all completed suicides (Figure 14.26; Mann, 2003). Bipolar patients are most at risk; about 20% of people who have been hospitalized for bipolar disorder commit suicide. And parents with mental illness are much more likely to have their adolescent children attempt to take their own lives (Santana et al., 2015). According to the *stress-diathesis model*, the suicidal individual has a predisposition, known as a diathesis, and then stress such as a worsening psychiatric condition acts as an environmental "straw that breaks the camel's back" (Mann, 2003).

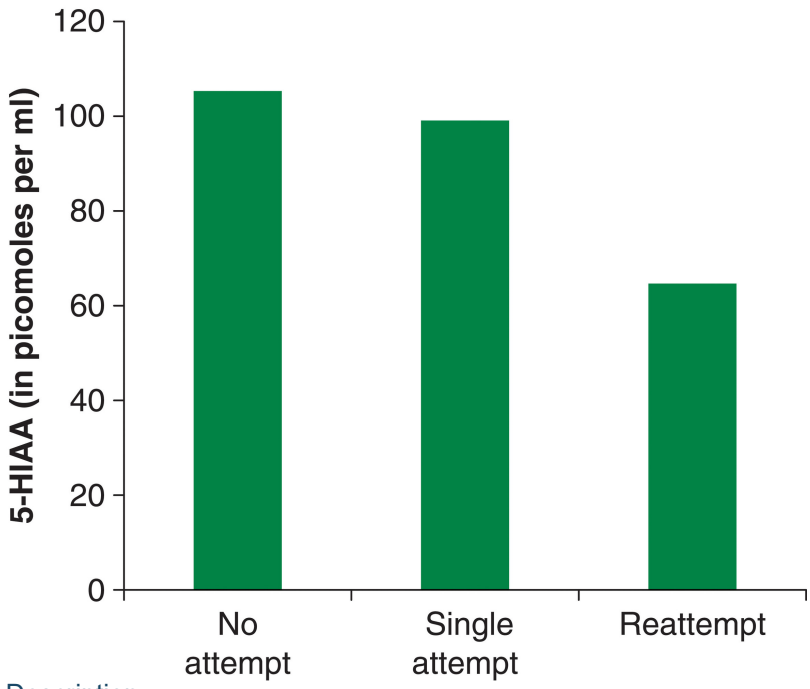


Description

Figure 14.26 Suicide Rates for Three Disorders in Men and Women.

Source: From "Catamnestic Long-Term Study on the Course of Life and Aging of Schizophrenics," by L. Ciompi, 1980, *Schizophrenia Bulletin, 6,* pp. 607–618, fig. 2, p. 610. Copyright © Oxford University Press. Used with permission.

The predisposition is at least partly genetic; a study of depressed patients located six chromosome sites that were associated with suicidal risk but independent of susceptibility for mood disorders (Zubenko et al., 2004). Psychiatric patients who attempt suicide also are more likely to have low levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) than non-attempters, which means that their serotonin activity is particularly decreased. When a group of patients at risk for suicide was followed for 1 year, 20% of those who were below the group median in 5-HIAA level had committed suicide; none of the patients above the median had (Träskman, Åsberg, Bertilsson, & Sjöstrand, 1981). Other studies have confirmed the association between lowered serotonin and suicidality (see Figure 14.27; Mann, 2003; Roy, DeJong, & Linnoila, 1989). Lowered 5-HIAA is found in suicide attempters with a variety of disorders and probably reflects impulsiveness rather than the patient's specific psychiatric diagnosis (Mann et al., 1990; Träskman et al., 1981); this view was supported by a later study in which impulsive suicide attempters were found to have lower 5-HIAA than either nonimpulsive attempters or controls (Spreux-Varoquaux et al., 2001). Genes for other neurological pathways and substances have also been linked to suicide, such as low brain-derived neurotrophic factors (required for neuronal survival), dopamine (also linked to impulsivity), and poor responses to stress (E. Lin & Tsai, 2016).



Description

Figure 14.27 Serotonin Levels and Suicide.
Serotonin level, as assessed by the metabolite 5-HIAA, was lower in depressed patients who attempted suicide than in those who did not, and even lower in those who reattempted.

Source: Based on data from Roy, DeJong, and Linnoila (1989).

However, antidepressants *can* increase the risk of suicide. A variety of explanations have been offered, including the agitation that often accompanies SSRI use (Fergusson et al., 2005) and disappointment over slow improvement and side effects (Mann, 2003). Concern about the vulnerability of children and adolescents resulted in a 22% decrease in SSRI prescriptions for youths in the United States and the Netherlands; unfortunately, this turned out to be a case of throwing out the baby with the bathwater, because youthful suicides increased 14% in the United States in 1 year and 49% in the Netherlands over 2 years (R. D. Gibbons et al., 2007). Some observers believe that the suicidal acts of individuals on antidepressants is the result of rebounding energy levels, which allow those with suicidal ideation the ability to carry out suicidal thoughts. Rather than reducing prescriptions wholesale, therapists need to be selective and to monitor their patients for suicidal tendencies.

Research has identified heritable characteristics that distinguish people at risk for suicide from others, referred to as *endophenotypes*. The most reproduced personality indicators have been impulsivity and aggression (Courtet, Gottesman, Jollant, & Gould, 2011). Disadvantageous decision making, indicated by measures such as the Iowa Gambling Task, suggest a prefrontal deficiency, and this has been verified in terms of reduced neural activity and altered prefrontal serotonergic functioning. The heritability of suicidal behavior (ideation as well as attempts) has been estimated in various studies at 38% to 55% (Brent & Melhem, 2008). Locating genes that predispose a person to suicide has been difficult, in part because of confounding with so many instigators to suicide; these include mental illness, physical illness, and life disappointments. Most studies have pointed to serotonin-related genes and genes involved with brain-derived neurotrophic factors, and a few other genes have been implicated, but there has been little confirmation (S.-J. Tsai, Hong, & Liou, 2011).

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- State the monoamine hypothesis; what is the evidence for it?
- How is affective disorder related to circadian rhythms?
- What brain differences are involved in the affective disorders?
- What are some of the factors in suicide?

ANXIETY, TRAUMA, AND STRESS-RELATED DISORDERS

As discussed in Chapter 8, anxiety is the anticipation of some future threat. Anxiety disorders include several illnesses. The major ones—phobia, generalized anxiety, and panic disorder—have lifetime risks of about 13%, 9%, and 6.8%, respectively (R. C. Kessler et al., 2012). But their significance lies less in their prevalence than in the disruptiveness of their symptoms. The panic disorder patient or the phobic patient may be unable to venture out of the house, much less hold down a job. Women show greater activation of limbic and attention areas during stressful events (Kogler, Gur, & Derntl, 2014) and are twice as likely as men to develop anxiety disorders (R. C. Kessler et al., 2009).

Heredity

Family and twin studies indicate that the anxiety disorders are genetically influenced, with heritability ranging between 30 and 50%, depending on the disorder (summarized in S. M. Meier & Deckert, 2019). Understanding the hereditary underpinnings of anxiety is difficult because of significant genetic overlap with other disorders. More than 94% of individuals with anxiety disorders have a history of other psychiatric problems (Gaderman, Alonso, Valagut, Zaslavsky, & Kessler,, 2012). The overlap with mood disorders is particularly strong; 50% to 60% of patients with major depression also have a history of one or more anxiety disorders (Kaufman & Charney, 2000), and panic disorder is found in 16% of bipolar patients (Doughty, Wells, Joyce, Olds, & Walsh, 2004). Some neural commonality between these two groups is suggested by the effectiveness of antidepressants in treating both mood disorders and anxiety disorders. The anxieties themselves appear to fall into three genetically related clusters, with generalized anxiety, panic, and agoraphobia (fear of crowds and open places) in one group; animal and situational phobias in the second; and social phobia overlapping genetically with both groups (Hettema, Prescott, Myers, Neale, & Kendler, 2005).

? What causes anxiety disorders?

Genetic research on anxiety disorders has most often implicated genes responsible for serotonin production, serotonin reuptake (like the HTTLPR portion of the *SLC6A4* serotonin transporter gene), and various subtypes of serotonin receptors (reviewed in P. E. Arnold, Zai, & Richter, 2004; S. M. Meier & Deckert, 2019; Rothe et al., 2004; You, Hu, Chen, & Zhang, 2005). Other leads include genes for monoamine oxidase (Tadic et al., 2003), for the adenosine receptor (P. E. Arnold et al., 2004; Lam, Hong, & Tsai, 2005), and for cholecystokinin and its receptor (P. E. Arnold et al., 2004). A more recent finding is that a gene expressed in white-matter connections between the cingulate cortex to other fear-related brain regions (*TMEM132D*) is abnormally overexpressed in individuals with anxiety disorders (Erhardt et al., 2012).

Generalized Anxiety, Panic Disorder, and Phobia

Anxiety is often confused with fear; however, as we saw in Chapter 8, fear is a reaction to real objects or stressors present in the environment, whereas anxiety involves anticipation of events or an inappropriate reaction to the environment. A person with generalized anxiety has a feeling of stress and unease most of the time and overreacts to stressful conditions. In panic disorder, the person has a sudden and intense attack of anxiety, with symptoms such as rapid breathing, high heart rate, and feelings of impending disaster. A person with a phobia experiences fear or stress when confronted with a situation—for instance, crowds, heights, enclosed spaces, open spaces, or specific objects, such as dogs or snakes.

Neurotransmitters

Benzodiazepines were the most frequently used anxiolytic (antianxiety) drugs in the past (Costall & Naylor, 1992) but now are considered a second line of defense because of their addiction potential. You may remember from our earlier discussion of drugs in Chapter 5 that benzodiazepines increase receptor sensitivity to the inhibitory transmitter gamma-aminobutyric acid (GABA), which is a major neurotransmitter target in treating anxiety. A deficit in benzodiazepine receptors may be one cause of anxiety disorder. Marczynski and Urbancic (1988) injected pregnant cats with a benzodiazepine tranquilizer. When the offspring were 1 year old, they were restless and appeared anxious in novel situations. When their brains were studied later, several areas of the brain had compensated for the tranquilizer by reducing the number of benzodiazepine receptors.

Anxiety also appears to involve lower activity at serotonin synapses (as we have mentioned earlier in this section). Antianxiety drugs initially suppress serotonin activity, but then they apparently produce a compensatory increase. The idea that a serotonergic increase is involved in anxiety reduction is supported by the fact that serotonin reuptake inhibitors are now the drugs of choice for treating anxiety and related disorders. Buspirone, a unique serotonin agonist, also is effective in alleviating anxiety with minimal side effects.

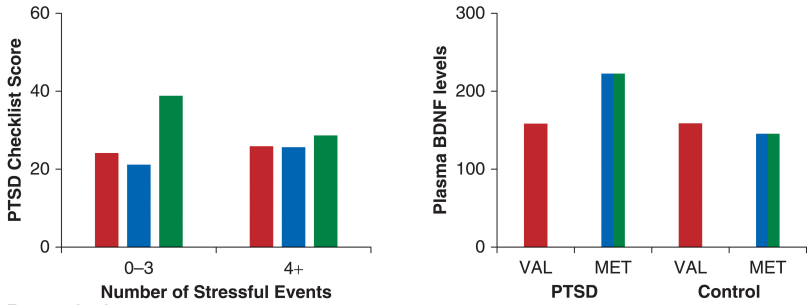
Finally, anxiety disorders can involve excess stimulation of norepinephrine receptors and the HPA axis (as we discussed in Chapter 8). Drugs that reduce the peripheral effects of norepinephrine, such as beta blockers and clonidine, can help alleviate the physical manifestations of stress and anxiety but may not alleviate the internal feelings of anxiety. As such, they are not prescribed primarily to treat these disorders.

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is a prolonged stress reaction to a traumatic event; it is typically characterized by recurrent thoughts and images of the traumatic event (flashbacks), avoiding reminders of the event, feelings of emptiness and detachment, lack of concentration, and overreactivity to environmental stimuli, such as loud noises. Individuals with PTSD frequently suffer from comorbid depression, panic attacks, and substance abuse. Each year, approximately 4% of U.S. adults are diagnosed with PTSD (Harvard Medical School, 2017). Because of news coverage, we usually associate PTSD with combat experiences, but it can be triggered by any form of trauma, including robbery, sexual assault, hostage situations, and automobile accidents. Men are more often exposed to such traumas, but women are almost three times as likely to develop PTSD when they do experience trauma (Harvard Medical School, 2017).

Drugs and traditional psychotherapy are not very effective in treating the more troublesome symptoms of re-experiencing and emotional numbing, but they are very helpful at alleviating the irritability, anger, and depression that accompany the disorder. Behavioral treatments such as exposure therapy are much more successful in general. In exposure therapy, the individual confronts anxiety-provoking stimuli in the safety of the therapist's office, for example, by repeatedly imagining the traumatic

event. Exposure therapy is essentially an extinction process, and fearful memories are notoriously resistant to extinction, especially in the 30% of people who have the *Val66Met* variation in the *BDNF* gene. Carriers of the *Met* allele have a smaller hippocampus volume than individuals with *Val/Val* alleles. In a study of Iraq and Afghanistan veterans with symptoms of probable PTSD, those with *Met/Met* alleles and who reported fewer than four lifetime stressful events had higher scores on a PTSD symptom checklist; *Met* made no difference in those who had a greater lifetime burden of stress. Those with either *Val/Met* or *Met/Met* configurations also had higher levels of *BDNF* (Figure 14.28; L. Zhang et al., 2014).



Description

Figure 14.28 Effect of *Val66Met* and *Met66Met* Alleles on PTSD and BDNF Levels. Left: Individuals with two *Met* alleles (green bars) and fewer stressful events had higher total PTSD Checklist scores than individuals with *Met/Val* (blue bars) or *Val/Val* (red bars) alleles. Right: In addition, having at least one *Met* allele increased the levels of the BDNF protein in PTSD individuals compared to control *Val/Val* participants.

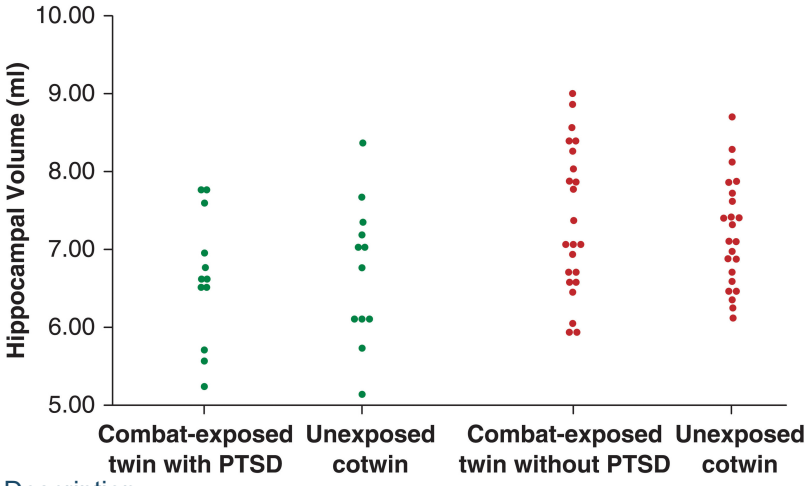
Source: Adapted from "PTSD risk is associated with *BDNF Val66Met* and *BDNF* overexpression" by L. Zhang et al. *Molecular Psychiatry, 19,* pp. 8–10. © 2014 Macmillan Publishers Limited.

In their search for better therapies, researchers are resorting to novel approaches; some, for example, believe that therapists could take a lesson from the phenomenon of reconsolidation that you learned about in Chapter 12. A team led by Daniela Schiller (2010) used a mild electric shock to condition an emotional reaction (measured by skin conductance response) to a blue square. A day later, the response was extinguished by repeatedly presenting the blue square alone. However, two subgroups of subjects received a "reminder" of the fear memory, one 10 minutes before extinction began and the other 6 hours before; the reminder was intended to start reconsolidation, a window of opportunity that was expected to remain open during extinction for the 10-minute group but to be closed by the time the 6-hour group's extinction trials began. It worked: The skin conductance response was almost entirely absent in the 10-minute group but had recovered to near training levels in the other two groups; the effect persisted for a year. Researchers hope this technique of *fear erasure* can be used to help relieve PTSD sufferers of their lingering fear and anxiety.

Anomalies in Brain Functioning

For the most part, the various anxiety disorders share a commonality of functional brain anomalies. Not surprisingly, the amygdala is hyperresponsive; the anterior cingulate cortex is hyperactive in general anxiety, panic disorder, and phobias, and the insular cortex is overly responsive in phobias and PTSD (Etkin & Wager, 2007; Morey et al., 2012; Shin & Liberzon, 2010). PTSD is distinguished by *decreased* activity in the medial prefrontal cortex and, according to some studies, in the hippocampus. Structures such as the hippocampus and amygdala have been reported to be smaller in people with anxiety disorders, particularly in those with PTSD (Logue et al., 2018). Researchers have usually assumed these variations were the result of the anxiety disorders, but we will see that this is not always the case.

Whether trauma is followed by PTSD is unrelated to either the severity of the traumatic event or the individual's distress at the time (A. G. Harvey & Bryant, 2002; Shalev et al., 2000); the key apparently is the person's vulnerability. Mark Gilbertson and his colleagues (2002) used magnetic resonance imaging to measure hippocampal volumes in Vietnam combat veterans and their noncombat identical twins. Those who suffered from PTSD had smaller hippocampi than did PTSD-free veterans, as expected, but so did the PTSD subjects' noncombat twins (Figure 14.29). Hippocampal reduction is often associated with childhood abuse, and Elizabeth Binder and her coworkers (2008) found that previously abused individuals were twice as likely to succumb to PTSD following traumatic events. Two mutations of the *FKBP5* gene are more common among PTSD patients who were abused and apparently contribute to the vulnerability (Binder et al., 2008). A smaller anterior cingulate cortex (ACC) may also be a vulnerability factor. After the Japanese earthquake and tsunami in 2011, researchers at Tohoku University asked 42 local residents who had previously received MRI scans to return and have their brains imaged again. Though none of the residents had full-blown PTSD, those with the highest scores had lower gray matter volumes in the orbitofrontal cortex and in the ACC, compared with control subjects (Sekiguchi et al., 2013). Reduced volume in the orbitofrontal cortex had occurred since the first scan, but the high-scoring subjects had lower ACC volume at the time of the first scan; this suggests that a smaller ACC is a vulnerability factor for PTSD. This makes sense, because the ACC is involved in the processing of fear and anxiety and in eliminating fear-related memories.

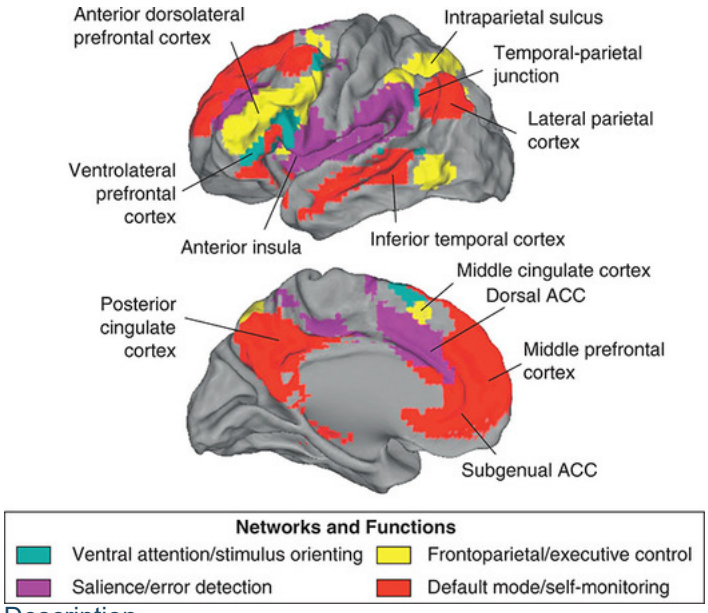


Description

Figure 14.29 Hippocampal Volume Is Reduced in Combat Veterans and Their Twins. Similar reduction in unexposed identical twins of PTSD patients suggests that hippocampal reduction is a predisposing factor.

Source: From "Smaller Hippocampal Volume Predicts Pathologic Vulnerability to Psychological Trauma," by M. W. Gilbertson et al., *Nature Neuroscience, 5,* pp. 1242–1247. Copyright © 2002 Nature Publishing Group. Used with permission.

Of course, these structures operate as part of circuits, rather than in isolation from each other or other parts of the brain. Chad Sylvester and his colleagues (2012) have identified four networks whose faulty performance they believe contributes to anxiety (Figure 14.30). The *ventral attention network* orients to attention-demanding stimuli and in people with anxiety disorders contributes to excessively stimulus-driven attention. Once a response to a situation is formulated, a *salience network* provides error detection by comparing the intended response with appropriate responses. A mismatch would signal the need for increased executive control, the domain of the *frontoparietal network*. Finally, the *default mode network* engages in self-monitoring, future planning, and emotion regulation; underactivity in this network results in poor emotional regulation. (We will return to some of these networks in Chapter 15.)



Description

Figure 14.30 Networks Involved in Anxiety.

Source: From "Functional Network Dysfunction in Anxiety and Anxiety Disorders," by C. Sylvester et al., 2012, *Trends in Neuroscience, 35*(9). With permission from Elsevier.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- What neurotransmitter deviations are involved in anxiety disorders?
- What neurological anomalies are associated with anxiety disorders?
- What are the environmental, physiological, and genetic contributors to PTSD?
- What are the networks that contribute to anxiety disorders?

PERSONALITY DISORDERS

The personality disorders are a group of 10 related disorders characterized by a relatively inflexible pattern of behavior that is different from one's peers, an onset around puberty to young adulthood, and distress or inability to function in society. Typical behavior patterns include distrust and suspicion (paranoid), unstable social and interpersonal relationships (asocial, avoidant, dependent, borderline), problems with control and attention (obsessive-compulsive), and emotional dysfunctions (histrionic, narcissistic). An abnormal psychology course will likely cover most of these personality disorders, but in this text we will concentrate on three types: obsessive-compulsive disorder (OCD), OCD-related disorders, and borderline personality disorder.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) consists of two behaviors, obsessions and compulsions, that occur in the same person. The disorder affects about 2.6% of the

population over their lifetimes (R. C. Kessler et al., 2012). An *obsession* is a recurring, uncontrollable thought; a person may be annoyed by a tune that mentally replays over and over or by troubling thoughts such as wishing harm to another person. Normal people have similar thoughts, but for the obsessive individual, the experience is extreme and feels completely out of control. Just as the obsessive individual is a slave to thoughts, the compulsive individual is a slave to actions. *Compulsions* are ritualistic behaviors that must be done to remove the anxiety of the obsession, such as touching a door frame three times before passing through the door, endless bathing and hand washing, or checking to see if appliances are turned off and the door is locked (Rapoport, 1991). Prominent examples of this disorder are depicted in the films *As Good as It Gets* and *The Aviator* and in the television show *Monk*. A Further Look describes three famous people with OCD or obsessive features.

A Further Look:

OCD and Mysophobia

Bettmann/Getty Images

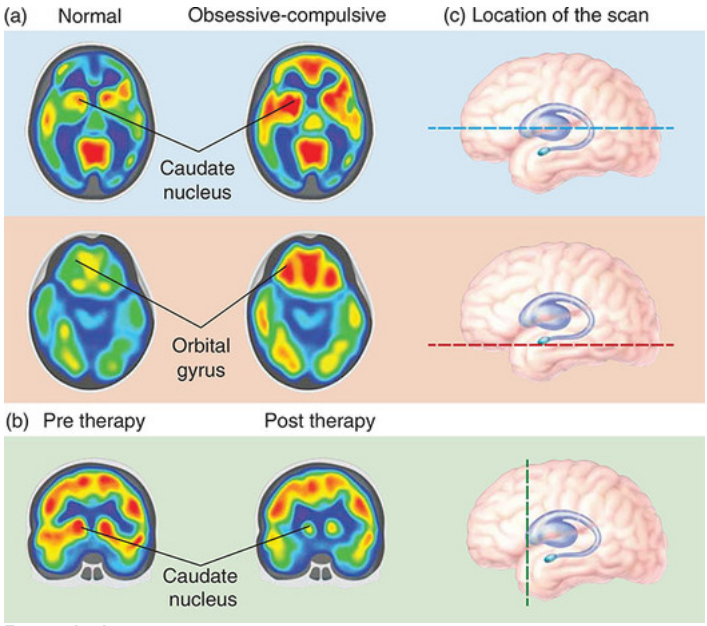
While many famous individuals can be eccentric, some unfortunately suffer from a personality disorder that makes their lives a constant struggle. Howie Mandel, the star of the television shows *Deal or No Deal* and *America's Got Talent*, suffers from OCD and a fear of germs, or mysophobia (Mandel, 2010). President Donald Trump admits to washing his hands as often as possible and drinking through a straw to avoid contamination (Sinclair, 2017). For Howard Hughes, the film tycoon, aircraft innovator, and business magnate whose life was chronicled in the movie *The Aviator*, OCD and a fear of germs were extremely debilitating. There were signs of disorder during Hughes's childhood, including a brief mysterious inability to walk, and his mother was obsessively concerned with germs, but his symptoms of OCD did not begin until after a series of airplane crashes and automobile accidents that left him almost unrecognizable. His mysophobia was so severe that assistants were required to handle his papers with gloves, sometimes several pairs, and he in turn grasped them with a tissue. He instructed his assistants never to touch him, talk directly to him, or even look at him; his defense for this behavior was that everybody carries germs and he wanted to avoid them (R. Fowler, 1986). When a business associate died, Hughes gave explicit instructions that flowers for the funeral were to be delivered by an independent messenger who would not have any contact with the florist or with Hughes's office—even to the point of sending a bill—to prevent "backflow" of germs (D. L. Bartlett & Steele, 1979).

What is obsessive-compulsive disorder, and what causes it?

One psychiatrist described a patient who tired of returning home to check whether she had turned her appliances off and solved the problem by taking her coffeemaker and iron to work with her (Begley & Biddle, 1996). The playwright and humorist David Sedaris (1998) wrote that his short walk home from school during childhood took a full hour because of his compulsion to stop every few feet and press his nose to the hood of a particular car, lick a certain mailbox, or touch a specific leaf that demanded his attention. Once home, he had to make the rounds of several rooms, kissing, touching, and rearranging various objects before he could enter his own room. About one fourth of OCD patients have a family member with OCD, suggesting a genetic involvement; boys are afflicted more often than girls, but the ratio levels off in adulthood (Swedo, Rapoport, Leonard, Lenane, & Cheslow, 1989).

What about individuals who are obsessed with neatness, organization, and generally making sure that their world is "where it should be"? This is not OCD but a related disorder called obsessive-compulsive personality disorder (OCPD), in which the person does not experience the distress and anxiety over obsessively cleaning and organizing that someone with OCD would experience. Instead, those feelings of perfection are perceived to be rational and reasonable. OCPD is much harder to treat, compared to OCD.

Imaging studies of OCD patients reveal increased activity in the orbitofrontal cortex, especially the left orbital gyrus, and in the caudate nuclei (Whiteside, Port, & Abramowitz, 2004). It is unclear whether these increases cause OCD or are merely activation increases associated with symptoms of OCD, such as worry. However, both drug treatment and behavior therapy reduce activation of the caudate nucleus and, in at least one study, the orbital gyrus (Figure 14.31; Porto et al., 2009; J. M. Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996; Swedo, Schapiro, et al., 1989). White matter reductions indicate that there are deficient connections between the cingulate gyrus and a circuit involving the basal ganglia, thalamus, and cortex, which apparently result in a loss of impulse control (Insel, 1992; Szeszko et al., 2005). An indication of dysfunction in this network is that orbitofrontal activity does not increase when OCD patients are required to reverse a previously correct choice; their unaffected relatives show the same deficit, suggesting that it is genetic (Chamberlain et al., 2008).



Description

Figure 14.31 Brain Structures Involved in Obsessive-Compulsive Disorder. Scans of OCD patients show that (a) activity is elevated in the caudate nucleus (a

part of the basal ganglia) and in the orbital gyrus and that (b) behavior therapy reduces this activity in the caudate nucleus.

Sources: (a) From "Local Cerebral Glucose Metabolic Rates in Obsessive Compulsive Disorder," by L. R. Baxter et al., 1987, *Archives of General Psychiatry, 44*(14), pp. 211–218. (b) From "Systematic Changes in Cerebral Glucose Metabolic Rate After Successful Behavior Modification Treatment of Obsessive-Compulsive Disorder," by J. M. Schwartz et al., 1996, *Archives of General Psychiatry, 53*(14), pp. 109–113.

OCD occurs with several diseases that damage the basal ganglia (Leonard et al., 1992), which, you will remember, are involved in motor activity. There is growing evidence that the disorder can be triggered in children by a bacterial infection that results in an autoimmune attack on the basal ganglia; vulnerability to the immune malfunction apparently is hereditary (P. D. Arnold & Richter, 2001; P. E. Arnold et al., 2004). OCD has also been reported in cases of head injury (McKeon, McGuffin, & Robinson, 1984).

Researchers believe that OCD patients are high in serotonergic activity. This was suggested by the fact that people with OCD are inhibited in action and feel guilty about aggressive impulses; sociopaths, by contrast, feel no guilt after committing impulsive crimes, and they have lowered serotonin activity. But the only drugs that consistently improve OCD symptoms are antidepressants that inhibit serotonin reuptake (Insel, Zohar, Benkelfat, & Murphy, 1990). So if OCD patients do have high serotonergic activity, then reuptake inhibitors must work by causing a compensatory reduction in activity; there is some evidence that treatment does decrease the sensitivity of serotonin receptors (Insel et al., 1990), but the nature of serotonin involvement remains uncertain (Graybiel & Rauch, 2000).

Patient response to serotonin reuptake inhibitors is usually only partial, and some patients do not respond at all; one third of these patients benefit from antipsychotics, and an antiglutamate drug produces modest relief (Abramowitz, Taylor, & McKay, 2009), suggesting the involvement of these transmitters. For treatment-resistant patients, psychosurgery is an option. Forty-seven percent of patients went into remission following cingulotomy, which involves lesioning the ACC, and another 22% improved (Sheth et al., 2013). A less drastic procedure is deep brain stimulation (DBS), targeting the internal capsule, a bundle of fibers that connect the frontal lobe with the thalamus and other areas. A DBS device was approved by the U.S. Food and Drug Administration (2009) after it produced a 40% reduction in symptoms in OCD patients. Following DBS treatment, patients reported less anxiety, better mood, and an improved feeling of self-confidence and self-reliance. The novel finding in this study was that individuals reported that they see the world as having more possibilities after DBS stimulation; they no longer must engage in their compulsions and can do more appropriate things instead (de Haan, Rietveld, Stokhof, & Denys, 2015).

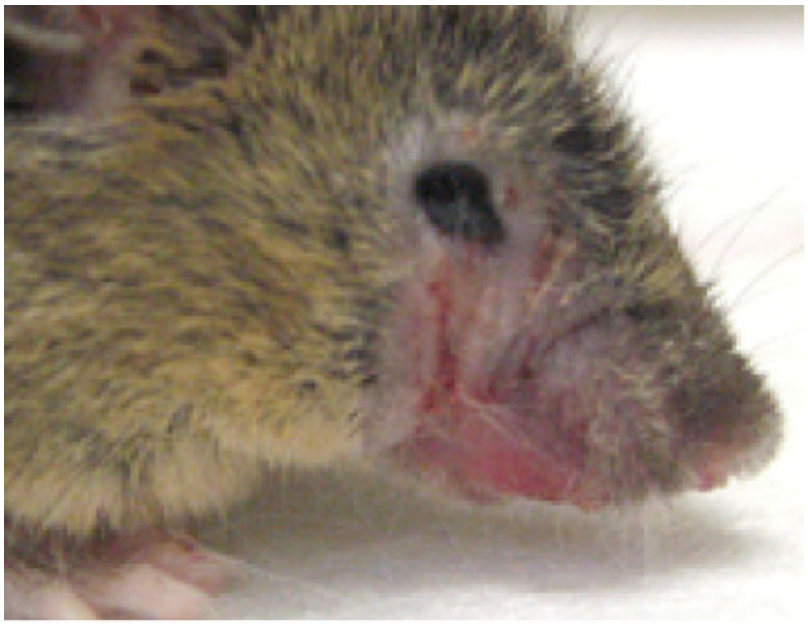
A meta-analysis of 113 studies found associations with two serotonin genes and, in males only, two genes involved in degradation of dopamine and serotonin (S. Taylor, 2013). There were trends for two dopamine-related genes and a glutamate-related gene, but these were not statistically significant. The rate of disorders in relatives of people with OCD suggests a genetic association with anxiety disorders, depression, tic disorders such as Tourette syndrome (discussed later), and grooming disorders such as hair pulling and skin picking (Bienvenu et al., 2012).

OCD-Related Disorders (Grooming and Hoarding)

The symptoms of OCD, particularly washing and "grooming" rituals and preoccupation with cleanliness, suggest to some researchers that it is a disorder of "excessive grooming" (Leonard, Lenane, Swedo, Rettew, & Rapoport, 1991; Rapoport, 1991). Dogs and cats sometimes groom their fur to the point of producing bald spots and ulcers in a disorder known as *acral lick syndrome*. Some chimpanzees and monkeys engage in excessive self-grooming and hair pulling, and 10% of birds in captivity compulsively pull out their feathers, occasionally to the point that the bird is denuded and at risk for infection and hypothermia. Clomipramine, an

antidepressant that inhibits serotonin reuptake, is effective in reducing all these behaviors (Grindlinger & Ramsay, 1991; Hartman, 1995; Rapoport, 1991).

If you think that the excessive grooming idea sounds far-fetched, consider the human behaviors of nail biting and obsessive hair pulling (trichotillomania), in which the person pulls hairs out one by one until there are visible bald spots or even complete baldness of the head, eyebrows, and eyelashes. There are several similarities between hair pulling and OCD: Both behaviors appear to be hereditary, and hair pullers have a high frequency of relatives with OCD; both symptoms also respond to serotonin reuptake inhibitors (Leonard et al., 1991; Swedo et al., 1991). However, trichotillomania and OCD sufferers appear to differ from each other in their versions of the *Sapap3* gene (Bienvenu et al., 2008). The gene's normal role is most likely a protective one, because mice that lack the gene groom to the point of self-injury (Figure 14.32); their behavior is relieved by a serotonin reuptake inhibitor (J. M. Welch et al., 2007).



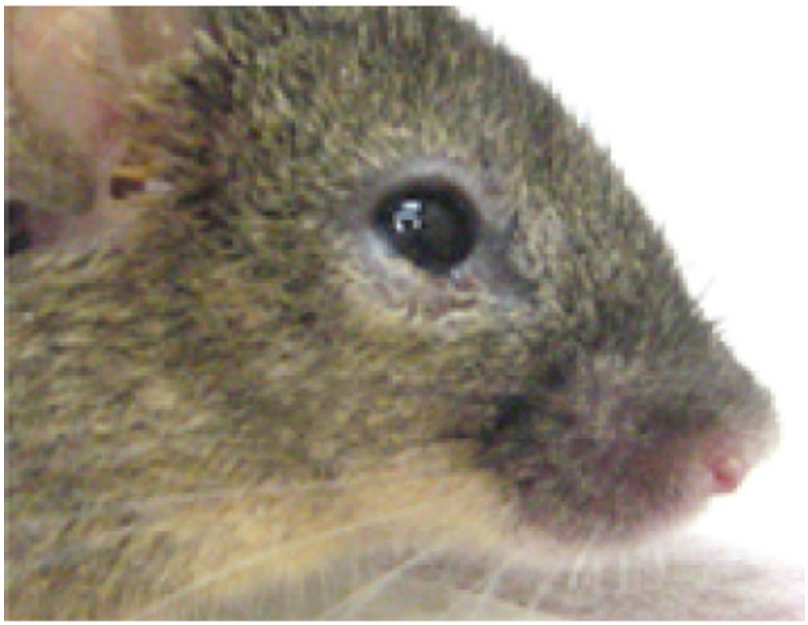
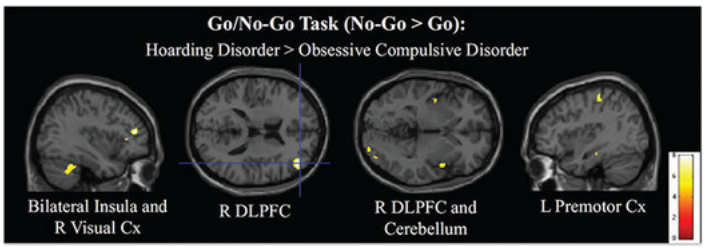


Figure 14.32 Excessive Grooming and the *Sapap3* Gene.
The mouse lacking the *Sapap3* gene (top) has groomed to the point of creating lesions on the neck and face and even damaging the eye.

Source: Courtesy of Jing Lu, Jeff Welch, and Guoping Feng.

Hoarders are dedicated collectors, stashing away just about anything from string to old newspapers. People with OCD are often hoarders as well, but hoarding disorder (HD) is considered distinct from OCD. David Tolin and his colleagues (2012) placed people with HD in an fMRI scanner and had them look at pictures of junk mail and newspapers and decide whether to keep or discard them. The subjects had brought 50 of the items from home, and another 50 were provided by the experimenters. Hoarders, people with OCD, and healthy controls all were willing to discard more than 40 of the 50 items that were not theirs. When it came to their own items, the healthy controls discarded 40 and those with OCD discarded 37, but the hoarders gave up only 29. More telling, during this part of the study, the hoarders reported "not feeling right" and showed more activity than the others in the ACC, which evaluates behavior and detects errors, and in the insula, which is important to a sense of self. Hoarders have more activity in the ACC and insula and the rest of the salience network than OCD patients, suggesting a problem with assessing the value of different choices and making good decisions (Figure 14.33; C. M. Hough et al., 2016).



Description

Figure 14.33 Hoarding Activates Different Brain Areas Than OCD.
Compared to OCD patients, hoarders had greater activation in salience network areas (insula, dorsolateral prefrontal cortex, cerebellum, and premotor areas) during a decision-making task. The salience network determines the value of objects and measures the consequences of actions, which suggests that hoarding is at least partially due to greater perceived value of objects than what they might actually be worth.

Source: Figure 2 from Hough, C. M., Luks, T. L., Lai, K., Vigil, O., Guillory, S., Nongpiur, A., et al. (2016). Comparison of brain activation patterns during executive function tasks in hoarding disorder and non-hoarding OCD. *Psychiatry Research: Neuroimaging, 255,* 50–59. © 2016 Elsevier Ireland Ltd. Used with permission.

Another disorder associated with OCD is **Tourette syndrome**, whose victims suffer from a variety of motor and phonic (sound) tics. They twitch and grimace, blink their eyes rapidly, throw punches at the air, cough, grunt, bark, echo what others say, mimic people's facial expressions and gestures, and (rarely) blurt out derogatory remarks and profanity. Both OCD and Tourette sufferers can manage their symptoms for short periods; for instance, Tourette patients are usually symptom free while driving a car, having sex, or performing surgery (yes, some of them are surgeons!). But neither OCD nor Tourette is a simple matter of will: Children often suppress compulsive rituals at school and "let go" at home, or they suppress tics during the day and then tic during their sleep. Neurologist Oliver Sacks (1990) graphically describes a woman on the streets of New York who was imitating other people's expressions and gestures as she passed them on the sidewalk:

> Suddenly, desperately, the old woman turned aside, into an alley-way which led off the main street. And there, with all the appearances of a woman violently sick, she expelled … all the gestures, the postures, the

> expressions, the demeanours, the entire behavioural repertoires, of the past forty or fifty people she had passed. (p. 123)

Symptoms begin between the ages of 2 and 15 years and usually progress from simple to more complex tics, with increasing compulsive or ritualistic qualities. The incidence of Tourette is difficult to determine; in recent studies, the numbers have varied from 3 to 8 per 1,000 persons. In a survey of 64,000 children in the United States, the rate was 3 out of every 1,000, with three times as many males as females (Scahill, Bitsko, Visser, & Blumberg, 2009). Tourette syndrome is genetically influenced, with a concordance rate of 53% for identical twins and 8% for fraternal twins (R. A. Price, Kidd, Cohen, Pauls, & Leckman, 1985). Tourette shares some genetic roots with OCD; one third of patients with early-onset OCD also have Tourette syndrome (do Rosario-Campos et al., 2005), and 30% of adults with Tourette are also diagnosed with OCD (R. A. King, Leckman, Scahill, & Cohen, 1998). Recent studies have identified a mutation of the *SLITRK1* gene in Tourette and found a mutation of the *Hdc* gene in a man and his eight offspring, all of whom have the disorder (Abelson et al., 2005; Ercan-Sencicek et al., 2010). The genes function in neural development and transmission, and both are highly active in brain areas involved in Tourette.

Tourette syndrome, like OCD, involves increased activity in the basal ganglia. But unlike OCD, the most frequently prescribed drug for Tourette is an antidopaminergic drug, haloperidol, though newer antidopamine drugs are also being used. One effect dopamine has is motor activation, and Malison and his colleagues (1995) found that dopamine activity is elevated in Tourette sufferers in the caudate nuclei of the basal ganglia (Figure 14.34). There has been some success treating Tourette with DBS to the thalamus, which suppressed tics and produced feelings of calmness (Okun et al., 2013).

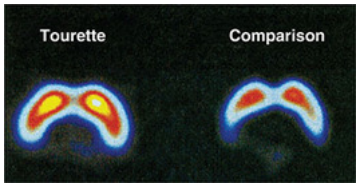


Figure 14.34 Increased Dopamine Activity in the Caudate Nuclei in Tourette Syndrome.
These two scans have not been superimposed over images of a brain; you can refer to Figure 14.31b to see where the caudate nuclei are located in the brain.

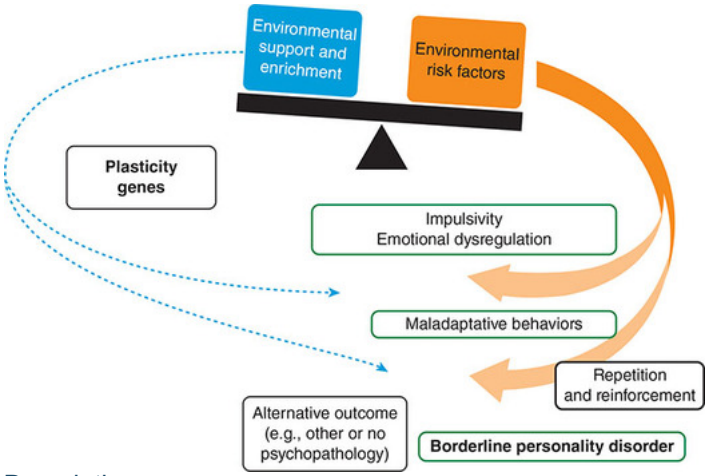
Source: From "[123I] α-CIT SPECT Imaging of Striatal Dopamine Transporter Binding in Tourette's Disorder," by R. T. Malison et al., 1995, *American Journal of Psychiatry, 152,* pp. 1359–1361. Copyright © 1995 American Psychiatric Publishing. Used with permission.

Borderline Personality Disorder

To finish up our tour of the psychological disorders, we end with one of the most intriguing personality disorders: borderline personality disorder (BPD). This condition, which affects 0.5 to 5.9% of the population (B. F. Grant et al., 2008), is characterized by unstable interpersonal relationships, poor self-image, and impulsivity. Individuals with this condition have an intense fear of abandonment and rejection and an equally strong desire to be loved. They often switch between intense feelings of "love" and "hate," they engage in risky behaviors such as gambling and speeding, and they are at a very high risk for suicide and suicidal thoughts. In fact, 8% to 10% of individuals with BPD kill themselves, and they are prone to taking medication far beyond the recommended dose in committing suicide.

BPD has a strong genetic basis, with a heritability of about 40% (Amad, Ramoz, Thomas, Jardri, & Gorwood, 2014). Genetic factors linked to BPD include genes that

influence neuronal survival (*BDNF*) and neuronal death, others that code for enzymes such as tyrosine hydroxylase that make up neurotransmitters, genes responsible for serotonin receptors, the *DAT1* dopamine transporter gene, and the 5-HTTLPR segment of the serotonin transporter gene (*SLC6A4*; reviewed in Amad et al., 2014). Therefore, BPD appears to be caused by dysfunction of both serotonin and dopamine neurotransmitter systems, as well as by decreases in neuronal number. Of interest was a finding that the *MAOA* gene (discussed in Chapter 8) is linked to both aggressive behaviors and BPD (I. W. Craig & Halton, 2009). Even with these genetic correlates, the remaining 60% of the disorder likelihood is environmental; indeed, psychiatrists believe the genes predispose an individual toward the imbalance of BPD but that a set of environmental events must occur as well to activate the epigenetic changes that can trigger the disorder (Figure 14.35).



Description

Figure 14.35 Integrative Model of Borderline Personality Disorder.
Environmental support can prevent the imbalances that cause epigenetic changes in plasticity genes and result in BPD (blue). Negative environmental experiences turn on genes that result in impulsivity and poor emotional control, which leads to the poor behavioral choices characteristic of the disorder.

Source: Figure 2 from "Genetics of borderline personality disorder: Systematic review and proposal of an integrative model," by A. Amad et al., 2014, *Neuroscience and Biobehavioral Reviews, 40,* pp. 6–19. Copyright © 2014 Elsevier. Used with permission.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- Describe the symptoms of OCD and the related disorders.
- What are the distinguishing characteristics of BPD?
- What treatments are used with these disorders?

IN PERSPECTIVE

The past several decades have seen enormous progress in research, and we now know a great deal about the physiological causes of disorders. We owe these breakthroughs to advances in imaging techniques and genetics research technology and to our greatly improved understanding of the physiology of synapses, not to mention the persistence of dedicated researchers. The result is that we can now

describe at the biological level many disorders that previously were believed to be "psychological" in origin or that were only suspected of having an organic basis.

Despite these great research advances, we cannot reliably distinguish the schizophrenic brain from a normal one or diagnose psychological disorders from a blood test. We may be able to someday, but in the meantime, we rely on changes in behavior of the individuals for a disorder diagnosis. This can be difficult, because these disorders frequently share common features (for example, schizophrenia, affective disorders with psychotic features, and bipolar I disorder all appear similar). We know, at least to some extent, the neurological changes that occur with mental illness, but we do not understand the unique combination of physiological and environmental factors that determines who will suffer from a disorder and who will not. Until we do, our treatments will remain a pale hope rather than a bright promise.

We have been reminded repeatedly that genetic vulnerability is not the same thing as fate. In most cases, the genes produce an illness only with the cooperation of the environment. This point is emphasized by the fact that psychotherapy and cognitive-behavioral therapy play an important role in treatment, enhancing and frequently exceeding the benefit that drugs can provide (see V. M. Durand & Barlow, 2006). While we search for genetic treatments of the disorders, we must remind ourselves once again that heredity is not destiny; improving the physical and psychological welfare of the population would go a long way toward preventing mental illness or reducing its severity.

Just before the dawning of this new age of research, one frustrated schizophrenia researcher concluded, "Almost everything remains to be done" (Heston, 1970, p. 254). Since then, our knowledge of both the brain and its participation in the symptoms of mental illness has increased dramatically, but as you can see, much of our understanding remains tentative. The pace is quickening, and we are confident that in this third decade of the new millennium, we will be celebrating even more impressive advances than in the past.

Chapter Summary

Schizophrenia

- Schizophrenia is characterized by a mix of positive and negative symptoms, such as hallucinations, delusions, thought disorder, and social and emotional withdrawal.
- Twin and adoption studies indicate that heritability is .80. Genetic influences involve many small-effect genes and rarer copy number variations with stronger effects. Genes apparently determine the level of vulnerability.
- Positive and negative symptoms may be distinguished by excess dopamine activity versus brain deficits.
- Although there is evidence for the dopamine hypothesis, it is an incomplete explanation. The glutamate hypothesis is getting more attention because NMDA receptor antagonists produce symptoms of schizophrenia, and substances that activate NMDA receptors relieve them.
- The brain irregularities include ventricular enlargement (due to tissue deficits), hypofrontality, and impaired connections; these apparently arise from prenatal insults and impaired postnatal development, in interaction with genetic vulnerability. Reduced connectivity and impaired synchrony between areas are also involved.
- Maternal effects from illnesses such as influenza and prenatal starvation are examples of environmental influences.

Affective Disorders

- The affective disorders include major depressive disorder (MDD), mania, and bipolar disorder, an alternation between mania and depression.
- The affective disorders are highly heritable, especially for women. Some genes are shared with schizophrenia, ASD, and ADHD.
- The most prominent explanation of affective disorders is the monoamine hypothesis—an imbalance in serotonin and epinephrine.
- Electroconvulsive therapy is a controversial but very effective last-resort therapy that has value when medications fail and as a temporary suicide preventative; both drugs and ECT increase neurogenesis and neural plasticity.
- People with affective disorders often have circadian rhythm disruptions. Others respond to circannual changes with winter depression or summer depression.
- Bipolar disorder is now considered to be a separate group of disorders and is the bridge disorder between schizophrenia and depression.
- Bipolar disorder is less understood than MDD. Response to atypical antipsychotics suggests involvement of dopamine and, possibly, serotonin.
- A number of neurological anomalies distinguish depressed people from bipolar patients and both from normal people.

- Depression, low serotonin activity, and several genes are associated with suicide risk.

Anxiety, Trauma, and Stress-Related Disorders

- The anxiety disorders are characterized mostly by brain hyperresponsiveness, but activity is decreased in some areas in posttraumatic stress disorder.
- Anxiety involves low serotonin activity; GABA transmission and benzodiazepine receptor deficiency may also be involved.
- The anxiety disorders are partially hereditary, and the serotonin system is most often implicated. There is considerable overlap with mood disorders.

Personality Disorders

- In obsessive-compulsive disorder, activity is increased in the orbitofrontal cortex; deficient connections with the cingulate gyrus apparently reduce impulse control.
- OCD is associated with grooming disorders, such as nail biting and hair pulling.
- Tourette syndrome shares some genetic roots with OCD, but OCD appears to involve high serotonin activity, whereas Tourette is treated with dopamine antagonists.
- In borderline personality disorder, there is a strong tendency for impulsivity, rapid emotional swings, and a series of damaging and maladaptive behaviors, such as gambling, speeding, and suicide.
- BPD is thought to occur through the epigenetic activation of genes related to serotonin, dopamine, and aggression systems.

Study Resources

For Further Thought

- Now that we are nearing the end of the text, summarize what you know about the interaction of heredity and environment. Give examples from different chapters and include the concept of vulnerability.
- Give an overall view of what produces deviant behavior (going back to earlier chapters as well as this one). What effect does this have on your ideas about responsibility for one’s behavior?
- Behavior is vulnerable to a number of disturbances, involving both genetic and environmental influences. Consider the different ways complexity of the brain contributes to this vulnerability.

Test Your Understanding

1. Explain the dopamine theory of schizophrenia. What are its deficiencies? What alternative or complementary explanations are available?
2. Describe the monoamine hypothesis of depression; include the evidence for it and a description of the effects of the drugs and ECT used to treat depression.

3. Describe the similarities and associations among OCD, Tourette, and grooming behaviors.

Select the best answer:

1. If you were diagnosed with schizophrenia, you should prefer ____ symptoms.
    1. positive
    2. negative
    3. chronic
    4. bipolar
2. The fact that schizophrenia involves multiple genes helps explain
    1. vulnerability to winter viruses.
    2. the onset late in life.
    3. positive symptoms.
    4. different degrees of vulnerability.
3. All drugs that are effective in treating schizophrenia
    1. interfere with reuptake of dopamine.
    2. have some effect at D_2 receptors.
    3. stimulate glutamate receptors.
    4. inhibit serotonin receptors.
4. Schizophrenia apparently involves
    1. tissue deficits.
    2. frontal dysfunction.
    3. disrupted connections.
    4. a and b
    5. a, b, and c
5. Which disorder is the bridge between schizophrenia and depressive disorders?
    1. Borderline personality disorder
    2. Obsessive-compulsive disorder
    3. Bipolar disorder
    4. Posttraumatic stress disorder
6. The monoamine hypothesis states that depression results from
    1. reduced activity in norepinephrine and serotonin synapses.
    2. increased activity in norepinephrine and serotonin synapses.
    3. reduced activity in norepinephrine, serotonin, and dopamine synapses.
    4. increased activity in norepinephrine, serotonin, and dopamine synapses.
7. ECT appears to relieve depression by
    1. producing amnesia for depressing memories.
    2. the same mechanisms as antidepressant drugs.
    3. punishing depressive behavior.
    4. increasing EEG frequency.
8. A frontal area hypothesized to switch between depression and mania is the
    1. dorsolateral prefrontal cortex.
    2. caudate nucleus.
    3. ventral prefrontal cortex.
    4. subgenual prefrontal cortex.
9. Studies indicate that risk for suicide is related to
    1. low norepinephrine and serotonin.
    2. high norepinephrine and serotonin.
    3. low serotonin.
    4. low norepinephrine.
10. The anxiety disorders are associated genetically with
    1. schizophrenia and depression.
    2. schizophrenia.
    3. depression.
    4. None of these
11. Of these, the best predictor of PTSD following trauma is
    1. a history of childhood abuse.
    2. being male.
    3. the severity of the trauma.
    4. the intensity of the reaction to the trauma.
12. Both OCD and Tourette syndrome involve compulsive rituals, probably because they involve

1. increased dopamine.
2. increased activity in the basal ganglia.
3. a stressful home life.
4. All of these

13. Instability of emotion is a hallmark of
    1. bipolar II disorder
    2. PTSD
    3. OCPD
    4. borderline personality disorder

Answers:

1. a, 2. d, 3. b, 4. e, 5. c, 6. a, 7. b, 8. d, 9. c, 10. c, 11. a, 12. b, 13. d.

For Further Reading

1. *When the Music's Over: My Journey Into Schizophrenia*, by Ross Burke (Plume/Penguin, 1995), is the author's account of his battle with schizophrenia, published by his therapist after Burke ended the battle with suicide.
2. *An Unquiet Mind*, by Kay Jamison (Knopf, 1995), tells the story of her continuing battle with bipolar disorder, which rendered her "ravingly psychotic" 3 months into her first semester as a psychology professor. With the aid of lithium, she has become an authority on mood disorders.
3. *Abnormal Psychology*, by William Ray (SAGE, 2015), is a text written with a neuroscience perspective.
4. *Here's the Deal: Don't Touch Me*, by Howie Mandel (Bantam, 2010), is a fascinating memoir of the comedian's lifelong struggle with OCD and the effect it has had not only on his own life but also on the lives of those around him.
5. "All in the Mind of a Mouse," by Carina Dennis (*Nature*, 2005, *438*, 151–152), is an intriguing look at the creative ways researchers are using mice to study human psychological disorders.
6. *I Hate You—Don't Leave Me*, by Jerold J. Kreisman (TarcherPerigee, 2010), is an amazing view into what someone with BPD goes through, written by a clinician who founded the world's first care facility specifically for individuals struggling with the disorder.
7. If you are interested in the most up-to-date description of medications currently being prescribed to combat various disorders, the *Handbook of Clinical Psychopharmacology for Therapists*, by John Preston and colleagues (8th ed., New Harbinger Publications, 2017), is a wonderful and inexpensive resource.

Key Terms

aberrant salience hypothesis 463

acute 459

bipolar disorder 474

chronic 459

circadian rhythm 481

circannual rhythm 481

depression 473

dopamine hypothesis 463

electroconvulsive therapy (ECT) 479

glutamate theory 466

incidence 458

lithium 483

major depressive disorder (MDD) 474

mania 474

monoamine hypothesis 476

negative symptoms 462

neuroleptics 464

obsessive-compulsive disorder (OCD) 492

phototherapy 482

positive symptoms 462

posttraumatic stress disorder (PTSD) 489

prevalence 458

psychosis 458

schizophrenia 458

seasonal affective disorder (SAD) 481

tardive dyskinesia 464

Tourette syndrome 496

vulnerability model 462

winter birth effect 470

Wisconsin Card Sorting Test 467

Descriptions of Images and Figures

Back to Figure

The horizontal axis is labeled Age of onset, and lists four age groups. The vertical axis is labeled Percentage of diagnoses, and ranges from 0 to 40, in increments of 10. The approximate data from the graph are tabulated below.

Back to Figure

The data from the graph and table are tabulated below.

Back to Figure

The horizontal axis is labeled Risk of schizophrenia in offspring in percentage, and ranges from 0 to 18 in increments of 2. The vertical axis lists different twins. The approximate data from the graph are tabulated below.

Back to Figure

The horizontal axis is labeled Average clinical dose for controlling schizophrenia in milligrams per day, and ranges from 0.1 to 1,000. The vertical axis is labeled Dosage necessary to block dopamine receptors in moles per liter, and ranges from 10 to

power of negative 10 to 10 to the power of negative 7. The approximate data from the graph are tabulated below.
Back to Figure

1. There are four scans. The first two scans show normal brain. In the left hemisphere, there is higher level of activity in the frontal lobe and occipital lobe and lower level of activity in the temporal lobe. In the right hemisphere, there is very high level of activity in the dorsolateral prefrontal cortex, high level of activity in the frontal lobe, low level of activity in the occipital lobe, and very low level of activity in the parietal lobe. The third and the fourth scans show schizophrenic brain. In the left hemisphere, there is very low level of activity in the frontal lobe, including the dorsolateral prefrontal cortex, and low level of activity in other regions. In the right hemisphere, there is very low level of activity in the dorsolateral prefrontal cortex, and low level of activity in other regions.
2. An illustration of the brain shows the dorsolateral prefrontal cortex in the frontal lobe of the brain.

Back to Figure

The first click is labeled S 1 and the second click is labeled S 2. For each click, the P 50 E E G wave shows a trough and a peak.

1. In controls, the size of the P 50 E E G wave is significantly reduced for S 2 than for S 1. In patients with schizophrenia, the size of the P 50 E E G wave is the same for both S 1 and S 2.
2. After treatment 1, the size of the P 50 E E G wave for S 1 is larger than that of S 2, which is of the same size as before treatment. After treatment 2, the size of the P 50 E E G wave for S 2 is smaller than that of S 1, which is of the same size as before treatment.

Back to Figure

The horizontal axis lists healthy volunteers and schizophrenia patients. The vertical axis is labeled interleukin-1 beta level, and ranges from 0 to 18 in increments of 2. In healthy volunteers (n equals 30), the interleukin-1 beta level for all volunteers were approximately 1. In schizophrenia patients (n equals 36), the level varied between 1 and 15, with an average of 4.5.

Back to Figure

a. The horizontal axis is labeled Month of year, and ranges from November to October in monthly increments. The vertical axis is labeled Average schizophrenic births, and ranges from 50 to 70 in increments of 10. The approximate data from the graph are tabulated below.

b. The horizontal axis is labeled Months after start of epidemic, and ranges from 0 to 11 in unit increments. The vertical axis is labeled Average schizophrenic births, and ranges from 50 to 68. The approximate data from the graph are tabulated below.

Back to Figure

The five moods are mania, hypomania, normal, mild depression, and major depression. The mood swings of individuals with different affective disorders are as follows.

- Bipolar disorder 1: Alternates between mania and major depression.
- Bipolar disorder 2: Alternates between hypomania and major depression.
- Cyclothymic disorder: Alternates between hypomania and mild depression.
- Major depressive disorder: Alternates between normal mood and major depression.

Back to Figure

a. A bar graph shows the formation of new cells when administered with vehicle and fluoxetine. The horizontal axis lists 5 days, 11 days, and 13 days. The vertical axis is labeled new cells as a percentage of vehicle group, and ranges from 0 to 180 in increments of 20. The approximate data from the graph are tabulated below.

b. A micrograph for vehicle shows arrows pointing toward S G Z and G C L. A micrograph for fluoxetine shows brown spots.

Back to Figure

1. Brain scans of the sagittal and coronal view of the brain show high activity in subgenual prefrontal cortex located in the anterior side of the brain.
2. A bar graph shows the mean metabolism in subgenual prefrontal cortex. The horizontal axis lists patients with different affective disorders. The vertical axis is labeled mean metabolism in subgenual prefrontal cortex, and ranges from 0.8 to 1.2 in increments of 0.1. The approximate data from the graph are tabulated below.

Back to Figure

The horizontal axis lists disorders. The vertical axis is labeled Suicide rate in percent, and ranges from 0 to 12 in increments of 2. The approximate data from the graph are tabulated below.

Back to Figure

The horizontal axis lists the suicide attempts. The vertical axis is labeled 5-H I A A in picomoles per milliliters, and ranges from 0 to 120 in increments of 20. The approximate data from the graph are tabulated below.

Back to Figure

In the first graph, the horizontal axis is labeled number of stressful events, listing 0 to 3 and 4 plus, and the vertical axis is labeled P T S D checklist score, ranging from 0 to 60 in increments of 20. The approximate data from the graph are tabulated below.

In the second graph, the horizontal axis lists the allele under P T S D and control and the vertical axis is labeled plasma B D N F levels, ranging from 0 to 300 in increments of 100. The approximate data from the graph are tabulated below.

Back to Figure

The vertical axis is labeled hippocampal volume in milliliters, and ranges from 5.00 to 10.00 in increments of 1.00.

For combat-exposed twin with P T S D, the plots are between 5.1 milliliters and 7.8 milliliters.

For unexposed cotwin, the plots are between 5.05 milliliters and 8.3 milliliters.

For combat-exposed twin without P T S D, the plots are between 6.00 milliliters and 9.00 milliliters.

For unexposed cotwin, the plots are between 6.0 milliliters and 8.8 milliliters.

Back to Figure

The networks and functions, and the structures associated with it are as follows.

- Ventral attention/stimulus orienting: Ventrolateral prefrontal cortex and temporal parietal junction.

- Salience/error detection: Anterior insula and dorsal anterior cingulate cortex.
- Frontoparietal/executive control: Anterior dorsolateral prefrontal cortex, intraparietal sulcus, and middle cingulate cortex.
- Default mode/self-monitoring: Inferior temporal cortex, lateral parietal cortex, posterior cingulate cortex, middle prefrontal cortex, and subgenual anterior cingulate cortex.

Back to Figure

1. Caudate nucleus in the basal ganglia and orbital gyrus in the frontal lobe show higher levels of activity in the brain of an individual with obsessive-compulsive disorder than in a normal brain.
2. The caudate nucleus shows lower level activity post therapy when compared with the activity pre therapy.
3. The location of the scan for different views are as follows. Caudate nucleus: Horizontally through the basal ganglia. Orbital gyrus: Horizontally through the temporal lobe. Post therapy: Vertically through the frontal lobe.

Back to Figure

The scans are titled, Go/No-Go Task (No-Go greater than Go): Hoarding Disorder greater than Obsessive compulsive disorder. The scans show the sagittal and transverse view of the brain. Few regions in bilateral insula, right visual cortex, right dorsolateral prefrontal cortex, cerebellum, and left premotor cortex show activation.

Back to Figure

The illustration shows that the occurrence of B P D is weighed down more by environmental risk factors when compared with environmental support and enrichment. Environmental support through plasticity of genes and environmental risk factors lead to impulsivity, emotional dysregulation, maladaptive behaviors, and repetition and reinforcement. These are the characteristics of borderline personality disorder or alternative outcome, for example other or no psychopathology.

15 SLEEP AND CONSCIOUSNESS

MONEY SHARMA/Staff/AFP/Getty Images

Sleep and Dreaming

- Circadian Rhythms
- Rhythms During Waking and Sleeping
- The Functions of Sleep
- Sleep, Plasticity, and Memory
- Brain Structures of Sleep and Waking
- Sleep Disorders

A Further Look | In the Still of the Night

- Sleep as a Form of Consciousness

Concept Check

The Neural Bases of Consciousness

Structural and Network Explanations of Consciousness

A Further Look | Determining Consciousness When It Counts

Awareness

Attention

The Sense of Self

Concept Check

In Perspective

Chapter Summary

Study Resources

After reading this chapter, you will be able to

15.1 Summarize the characteristics of the rhythms that occur during sleep and waking.

15.2 Describe the neural controls of sleep and waking rhythms.

15.3 Examine the functions of sleep and shorter rhythms.

15.4 Assess the causes of sleep disorders.

15.5 Explain how researchers are approaching the issue of consciousness.

15.6 Indicate the neural processes that contribute to consciousness.

Kenneth Parks got up from the couch where he had been sleeping and drove 14 miles to his in-laws' home. There he struggled with his father-in-law before stabbing his mother-in-law repeatedly, killing her. He then drove to the police station, where he told the police that he thought he had "killed some people." In court, his defense was that he was sleepwalking. Based on the testimony of sleep experts and the lack of motive—Ken had an affectionate relationship with his in-laws—the jury acquitted him of murder (Broughton et al., 1994).

Were Ken's actions possible for someone who was sleepwalking? Was he really asleep and therefore not responsible? This case raises the question of what we mean by *consciousness*. Many psychologists, and especially neuroscientists, avoid the topic because they think that consciousness is inaccessible to research. This has not always been so; consciousness was a major concern of the fledgling discipline of psychology near the end of the 19th century. But the researchers' technique of *introspection* was subjective: The observations were open only to the individuals doing the introspecting, who often disagreed with each other. This failing encouraged the development of behaviorism, which was based on the principle that psychology should study only the relationships between external stimuli and observable responses. Behaviorism was a necessary means of cleansing psychology of its subjective methods, but its purge discarded subject matter along with the methodology. The interests of psychologists would not shift back to include internal

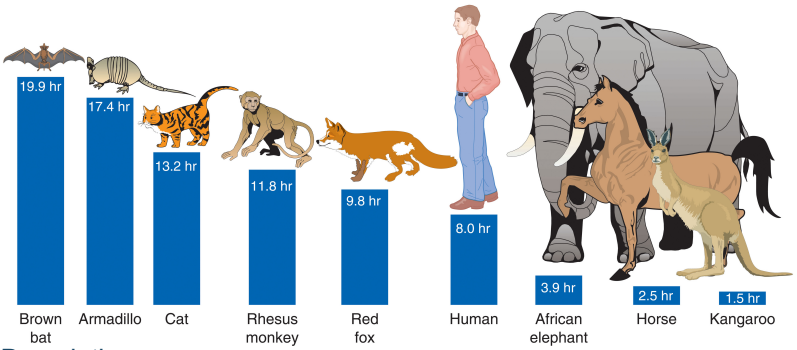
experience until the emergence of the field of *cognitive psychology* in the 1950s and 1960s.

Many cognitive psychologists were finding it difficult to understand psychological functions such as learning and perception without taking account of various aspects of consciousness. Still, few of them tackled the subject of consciousness itself. The problem seemed too big, there was no clear definition of consciousness, and the bias that consciousness was a problem for philosophers still lingered. Gradually, some of them began to ally themselves with philosophers, biologists, and computer experts to develop new research strategies for exploring this last frontier of psychology. The greatest inroads have been made in the study of sleep, largely because sleep is readily observable. Also, because sleep is open to study by objective techniques, it has not had the stigma among researchers that characterizes other aspects of consciousness. We will begin this last leg of our journey with the topic of sleep and dreaming.

SLEEP AND DREAMING

Each night, we slip into a mysterious state that is neither entirely conscious nor unconscious. Sleep has intrigued humans throughout history: Metaphysically, dreaming suggested to our forebears that the soul took leave of the body at night to wander the world; practically, sleep is a period of enforced nonproductivity and vulnerability to predators and enemies.

In spite of thousands of research studies, we are still unclear on the most basic question: What is the function of sleep? The most obvious explanation is that sleep is *restorative*. Support for this idea comes from the observation that species with higher metabolic rates typically spend more time in sleep (Zepelin & Rechtschaffen, 1974). A less obvious explanation is the *adaptive* hypothesis; according to this view, the amount of sleep an animal engages in depends on the availability of food and on safety considerations (Webb, 1974). Elephants, for instance, which must graze for many hours to meet their food needs, sleep only briefly. Animals with low vulnerability to predators, such as the lion, sleep much of the time, as do animals that find safety by hiding, such as bats and burrowing animals. Vulnerable animals that are too large to burrow or hide—for example, horses and cattle—sleep very little (Figure 15.1). In a study of 39 species, the combined factors of body size and danger accounted for 80% of the variability in sleep time (Allison & Cicchetti, 1976).



Description

Figure 15.1 Time Spent in Daily Sleep for Different Animals.
Observations support the hypothesis that sleep is an adaptive response to feeding and safety needs.

Source: Based on data from "Animal Sleep: A Review of Sleep Duration Across Phylogeny," by S. S. Campbell and I. Tobler, 1984, *Neuroscience and Biobehavioral Reviews*, *8*, pp. 269–300.

Why do we sleep?

? Whatever the function of sleep may be, its importance becomes apparent when we look at the effects of sleep deprivation. These effects are nowhere more evident than in shift work. Shift workers sleep less than day workers, and their work performance suffers as a result (Tepas & Carvalhais, 1990). Also, they typically fail to adjust their sleep-wake cycles adequately, because their sleep is disturbed during the day and they conform to the rest of the world's schedule on weekends. With their work and sleep schedules at odds with their biological rhythms, shift workers find that sleep intrudes into their work and that daytime arousal interferes with their sleep. Another study with mice may give us a clue as to why this happens. After just a few days of sleeping 3 to 5 hours per day, the mice had lost 25% of the neurons in the locus coeruleus, a part of the brain that is important for alertness (J. Zhang et al., 2014).

In long-term sleep deprivation studies, impairment follows a rhythmic cycle—performance declines during the night and then shows some recovery during the daytime (Horne, 1988). The persistence of this rhythm represents a safety hazard of gigantic proportions when people try to function at night. The largest number of single-vehicle traffic accidents attributed to "falling asleep at the wheel" occur around 2 a.m. (Mitler et al., 1988), and the number of work errors peaks at the same time (Broughton, 1975). In addition, the Three Mile Island nuclear plant accident took place at 4 a.m.; the Chernobyl nuclear plant meltdown began at 1:23 a.m.; the Bhopal, India, chemical plant leakage, which poisoned more than 2,000 people, began shortly after midnight; and the *Exxon Valdez* ran aground at 12:04 a.m., spilling 11 million gallons of oil into fragile Alaskan waters (Alaska Oil Spill Commission, 1990; Mapes, 1990; Mitler et al., 1988). Even the annual switch to daylight saving time is so disruptive that eliminating it would, according to one estimate, reduce commute time vehicle fatalities by 3% and pedestrian deaths during the same time periods by 13%, saving 366 lives each year (Coate & Markowitz, 2004).

Travel across time zones also disrupts sleep and impairs performance, particularly when you travel eastward. It is difficult to quantify the effects of *jet lag*, but three researchers attempted to do so in a novel way by comparing the performance of baseball teams. When East Coast and West Coast teams played at home, their percentage of wins was nearly identical—50% and 49%, respectively. When they traveled across the continent but had time to adjust to the new time zone, they showed a typical visitor's disadvantage, winning 45.9% of their games. Teams traveling west without time to adjust won about the same, 43.8% of their games, whereas teams traveling east won only 37.1% (Recht, Lew, & Schwartz, 1995). Sleep quality is better when you extend the day's length by traveling west, rather than shorten it as you do when you travel east. One way of looking at this effect is that it is easier to stay awake past your bedtime than it is to go to sleep when you are not sleepy. We will examine a more specific explanation in the next section, when we consider circadian rhythms.

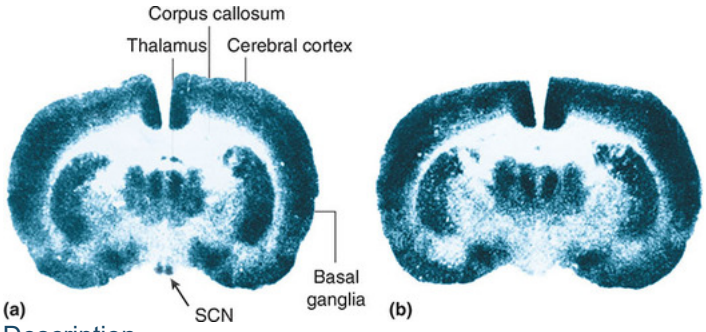
Circadian Rhythms

We saw in Chapter 14 that a *circadian rhythm* is a rhythm that is about a day in length; the term *circadian* comes from the Latin *circa*, meaning "approximately," and *dia*, meaning "day." We operate on a 24-hour cycle, in synchrony with the solar day. We sleep once every 24 hours, and body temperature, alertness, urine production, steroid secretion, and a variety of other activities decrease during our normal sleep period and increase during our normal waking period, even when we reverse our sleep-wake schedule temporarily.

? Why are circadian rhythms important?

The main biological clock that controls these rhythms in mammals is the **suprachiasmatic nucleus (SCN)** of the hypothalamus. Lesioning the SCN in rats abolishes the normal 24-hour rhythms of sleep, activity, body temperature, drinking, and steroid secretion (Abe, Kroning, Greer, & Critchlow, 1979; Stephan & Nunez, 1977). The SCN is what is known as a *pacemaker*, because it keeps time and regulates the activity of other cells. We know that the rhythm arises in the SCN,

because rhythmic activity continues in isolated SCN cells (Earnest, Liang, Ratcliff, & Cassone, 1999; Inouye & Kawamura, 1979). Lesioned animals do not stop sleeping, but instead of following the usual day-night cycle, they sleep in naps scattered throughout the 24-hour period. So the SCN controls the timing of sleep, but sleep itself is controlled by other brain structures, which we will discuss later. The SCN is shown in Figure 15.2, and you can check Figure 6.2 to see its location.



Description

Figure 15.2 The Suprachiasmatic Nucleus.
(a) The nuclei, indicated by the arrows, took up more radioactive 2-deoxy-glucose in the scan because the rat was injected during the "light-on" period of the day; (b) the rat was injected during the "light-off" period.

Source: Reprinted with permission from W. J. Schwartz and H. Gainer, "Suprachiasmatic Nucleus: Use of 14C-labeled Deoxyglucose Uptake as a Functional Marker," *Science*, *197*, 1089–1091. Copyright 1977 American Association for the Advancement of Science.

The SCN is *entrained* to the solar day by cues called *zeitgebers* ("time-givers"). If humans are kept in isolation from all time cues in an underground bunker or a cave, they usually lose their synchrony with the day-night cycle; in many studies, zeitgeber-deprived individuals "drifted" to a day that was about 25 hours long, with a progressively increasing delay in sleep onset (Figure 15.3; Aschoff, 1984). For a long time, researchers believed that alarm clocks and the activity of others were the most important influences that entrain our activity to the 24-hour day, but research points more convincingly to light as the primary zeitgeber.

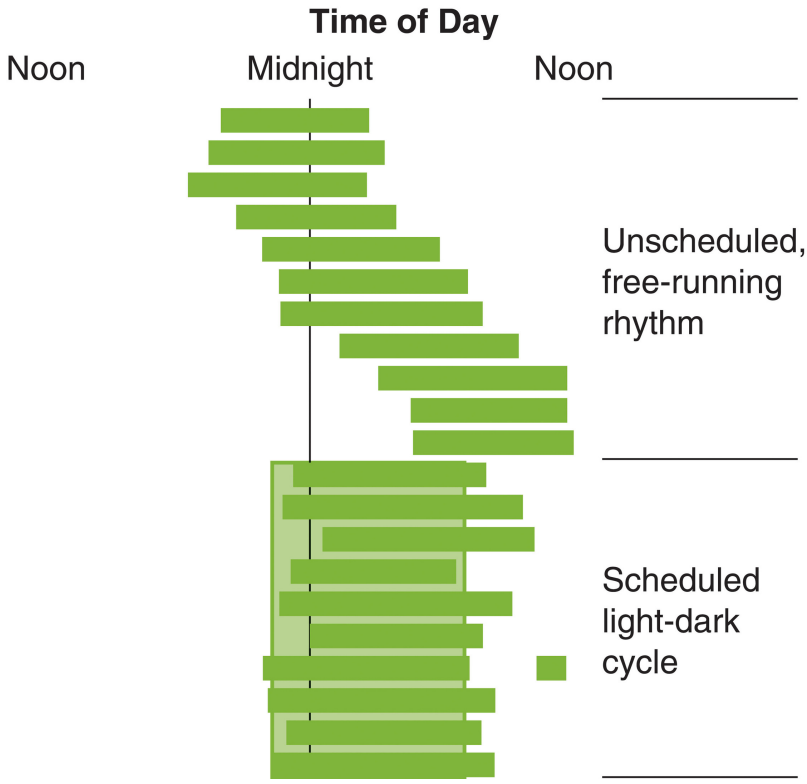


Figure 15.3 Sleep and Wake Periods During Isolation From Time Cues.
Each green bar indicates the timing and length of sleep during a day. During the unscheduled period (without time cues), the subject's activity assumed a 25-hour rhythm and began to advance around the clock. When light-dark periods were scheduled, he resumed a normal sleep and activity rhythm.

Source: Introduction to Psychology, Gateways to Mind and Behavior (with InfoTrac) 11th edition, by D. Coon and John O. Mitterer, 2007. Reprinted with permission of Wadsworth, a division of Thomson Learning. Based on Czeisler et al., 1981.

The *difference* in light intensity between the light and dark periods is important for entraining the day-night cycle. One group of night workers worked under bright lights and slept in complete darkness during the day (*light discrepant*); a second group worked under normal light and slept in the semidarkness that is typical of the day sleeper (*similar light*). The light-discrepant workers scored higher in performance and alertness than the similar-light workers. Their physiological measures also synchronized with the new sleep-wake cycle; for example, their body temperature dropped to its low value around 3:00 p.m., when they were asleep, but the similar-light group's low continued to occur at 3:30 a.m. in spite of being awake and working (Czeisler et al., 1990). If you're thinking the take-home from this study is that you should keep the lights as bright as possible when you're awake, you would be wrong. Compared with dim light, exposure to normal room light for the 8-hour period before bedtime reduces the duration of melatonin release by 90 minutes each night (Gooley et al., 2011). **Melatonin** is a hormone that induces sleepiness. The typically sleep-deprived state in modern society appears to be due in part to living under bright lights and spending evenings staring at a TV, computer, or phone, whose blue light–emitting screens particularly reduce melatonin production and disrupt sleep (L. Hale et al., 2018).

Just how much we rely on a regular lighting schedule for entrainment was underscored in a study of four Greenpeace volunteers living in isolation during the 4-month darkness of the Antarctic winter; their sleep times and physiological measures free-ran on a roughly 25-hour interval, even though they had access to time information and social contact with each other (Kennaway & van Dorp, 1991).

According to some observers, it is this “slow-running” clock that makes phase delays (going to sleep later) easier than phase advances (going to sleep earlier). So adjustment after westward travel is easier than after traveling east, and workers who rotate shifts sleep better and produce more if the rotation is to later shifts rather than to earlier ones (Czeisler, Moore-Ede, & Coleman, 1982). Some people seem to be relatively insensitive to the environmental cues that entrain most of us to a 24-hour day and tend to operate on a 25-hour clock; and like a clock that runs too slowly, their physical and cognitive functioning moves in and out of phase with the rest of the world, resulting in insomnia and impaired functioning.

Why the internal clock would operate on a 25-hour cycle is unclear, especially because animals kept in isolation typically run on a 24-hour cycle (Czeisler et al., 1999). Some researchers have suggested that it has something to do with the 24.8-hour lunar cycle, which influences the tides and activity cycles of a number of marine species (Tessmar-Raible, Raible, & Arboleda, 2011). However, research has not found a relationship between the lunar cycle and any human rhythm (Foster & Roenneberg, 2008). Czeisler and his colleagues (1999) suggested that the 25-hour cycle in isolation studies is an artifact of allowing the individuals to control the room lighting. Bright light late in the day causes the cycle to lengthen, so Czeisler kept the light at a level that was too low to influence the circadian rhythm while people lived on a 28-hour sleep-wake schedule. Under that condition, their body temperature cycle averaged 24.18 hours, which led Czeisler to conclude that the *biological* rhythm is approximately 24 hours long.

The SCN controls the production of melatonin, and light resets the biological clock every day by suppressing melatonin secretion (Boivin, Duffy, Kronauer, & Czeisler, 1996). However, about one third of totally blind people suppress melatonin production in response to light and entrain to the light-dark cycle (J. T. Hull, Czeisler, & Lockley, 2018). Mice lacking rods and cones also show normal entrainment and cycling, so the signal must arise from some other retinal light receptors (Freedman et al., 1999; Lucas, Freedman, Muñoz, Garcia-Fernández, & Foster, 1999). Ganglion cells ordinarily receive information about light from the visual receptors, but about 1% of ganglion cells respond to light directly and send their information to the SCN via the retinohypothalamic pathway (Hattar, Liao, Takao, Berson, & Yau, 2002). These ganglion cells contain melanopsin, which is a light-sensitive substance, or photopigment (Dacey et al., 2005; Panda et al., 2005; Qiu et al., 2005). The melanopsin is located in their widely branching dendrites, which suits the cells for detecting the overall level of light, as opposed to contributing to image formation (Figure 15.4). A study has confirmed that some ganglion cells in human retinas contain melanopsin (Dkhissi-Benyahya, Rieux, Hut, & Cooper, 2006). Interestingly, there is evidence that variations in the *Opn4* melanopsin gene result in reduced melanopsin and account for about 5% of cases of seasonal affective disorder (see Chapter 14); presumably this is because the individual responds inadequately to low winter light levels (Roecklein et al., 2009; Roecklein et al., 2013).

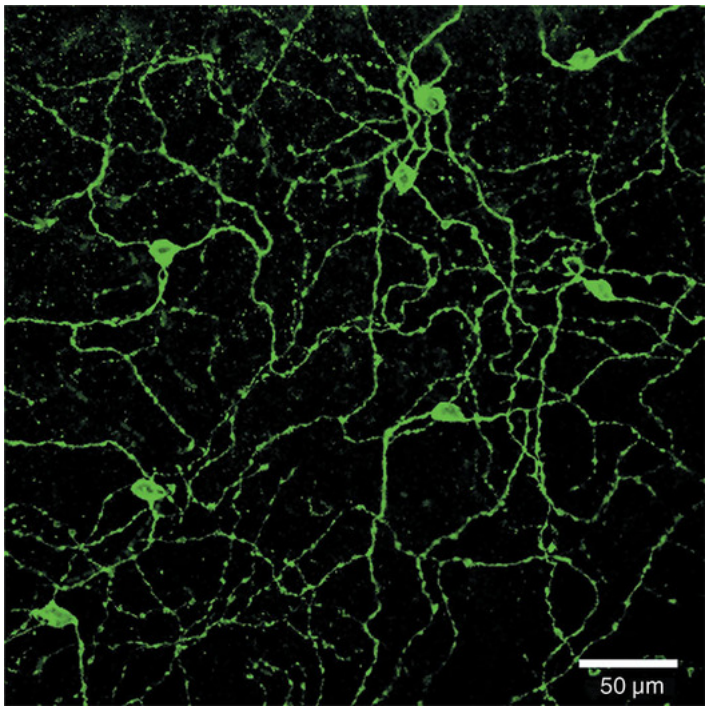


Figure 15.4 Retinal Ganglion Cells Containing Melanopsin.
The cells were labeled with a fluorescent substance that reacts to melanopsin. Notice the widespread dendrites, which contain melanopsin.

Source: From "Melanopsin-Containing Retinal Ganglion Cells: Architecture, Projections, and Intrinsic Photosensitivity," by S. Hattar, H. W. Liao, M. Takao, D. M. Berson, and K. W. Yau, *Science*, *295*, pp. 1065–1070. © 2002 American Association for the Advancement of Science (AAAS). Reprinted with permission from AAAS.

Nearly all organisms follow a circadian rhythm; the rhythm is based on an internal clock consisting of a few genes and their protein products (Andreani, Itoh, Yildirim, Hwangbo, & Allada, 2015; Rijo-Ferreira & Takahashi, 2019); the genes fall into two groups, one group that is turned on while the other is turned off. When the genes are on, their particular protein products build up. Eventually, the accumulating proteins turn off their genes, and the other set of genes is turned on. This feedback loop provides the approximately 24- or 25-hour cycle, which then must be reset each day by light. This process is not limited to neurons in the SCN; there are additional clocks, located outside the brain and controlling the activities of the body's organs (Hastings, Reddy, & Maywood, 2003). These clocks operate independently of the SCN, but the SCN entrains them to the day-night cycle. Feeding is an example of an activity that is controlled independently. According to the researchers, local clocks that affect blood pressure and heart activity explain why there is a large increase in the risk of heart attack, stroke, and sudden cardiac death after waking in the morning. Disruption of circadian rhythms is associated with sleep disorders, cancer, vulnerability to infections, and Alzheimer's disease (Rijo-Ferreira & Takahashi, 2019).

Rhythms During Waking and Sleeping

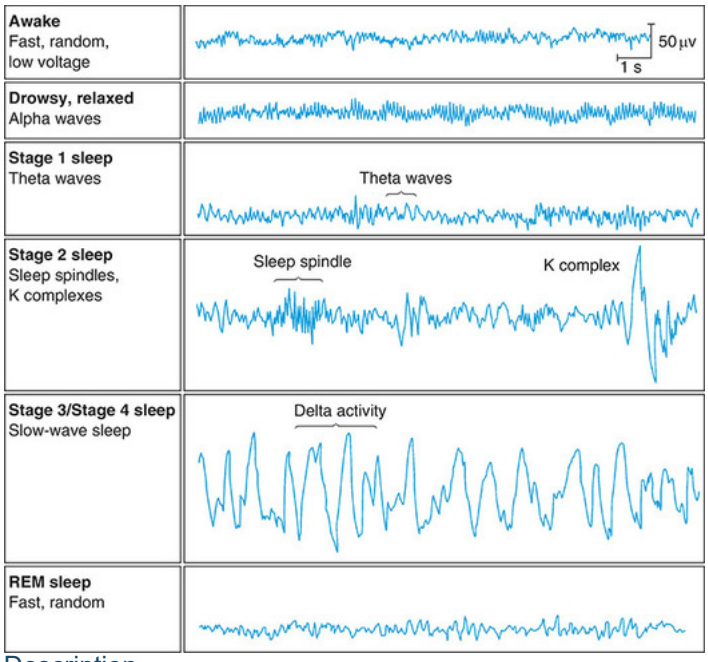
Riding on the day-long wave of the circadian rhythm are several ultradian rhythms. An **ultradian rhythm** is shorter than a day in length. Hormone production, urinary output, alertness, and other functions follow regular cycles throughout the day. For example, the dip in alertness and performance in the wee hours of the morning is mirrored by another in the early afternoon, which cannot be accounted for by post-lunch sleepiness, because it also occurs in people who skip lunch (Broughton, 1975). Incidentally, this dip coincides with the time of siesta in many cultures and a rest

period in nonhuman primates. The *basic rest and activity cycle* is a rhythm that is about 90 to 100 minutes long. When people wrote down what they were thinking every 5 minutes for 10 hours, the contents showed that they were daydreaming on a 90-minute cycle; electroencephalogram (EEG) recordings verified that these were periods of decreased brain activity (Kripke & Sonnenschein, 1973). Alertness is not the only function affected by this 90-minute cycle; the same cycling has been seen in other physiological measures of arousal, including heart rate, EEG, and pupillary diameter (Lavie, 2012).

? What rhythms occur throughout the day and night?

The common view of sleep is that it is a cessation of activity that occurs when the body and brain become fatigued. Sleep, however, is an active process. This is true in two respects. First, you will soon see that sleep is a very busy time; a great deal of activity goes on in the brain. Second, sleep is not like a car running out of gas but instead is turned on by brain structures and later turned off by other structures.

The most important measure of sleep activity is the EEG. When a person is awake, the EEG is a mix of *alpha* and *beta* waves. Alpha waves are activity whose voltage fluctuates at a frequency of 8 to 12 hertz (Hz) and moderate amplitude; beta has a frequency of 13 to 30 Hz and a lower amplitude. Beta waves, which are associated with arousal and alertness, are progressively replaced by alpha waves as the person relaxes (Figure 15.5). It may seem strange that the amplitude of the EEG is lower during arousal. Remember that the EEG is the sum of the electrical activity of all the neurons between the two recording electrodes. When a person is cognitively aroused, neurons under the electrodes are mostly desynchronized in their firing as they carry out their separate tasks; with the neurons firing at different times, the EEG has a high frequency, but the amplitude is rather low. As the person relaxes, the neurons have less processing to do and fall into a pattern of synchronized firing. The rate is low, but the cumulative amplitude of the neurons firing at the same time is high.



Description

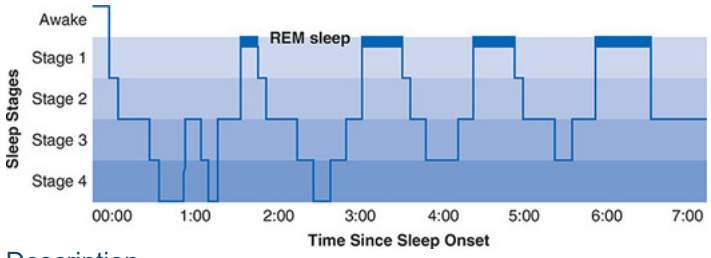
Figure 15.5 Electroencephalogram and the Stages of Sleep.

Source: From *Current Concepts: The Sleep Disorders*, by P. Hauri, 1982, Kalamazoo, MI: Upjohn.

As the person slips into the light first stage of sleep, the EEG shifts to *theta* waves, with a frequency of 4 to 7 Hz (Figure 15.5). About 10 minutes later, Stage 2 begins,

indicated by the appearance of *K complexes* and *sleep spindles*. K complexes are sharp, large waves that occur about once per minute; sleep spindles are brief bursts of 12- to 14-Hz waves that appear to serve a gating function, preventing disruptive stimuli from reaching the cortex and waking the sleeper (Dang-Vu, McKinney, Buxton, Solet, & Ellenbogen, 2010). Stages 3 and 4 are known as **slow-wave sleep** and are characterized by large, slow delta waves at a frequency of 1 to 3 Hz. The person moves around in bed during this period, turning over and changing positions. Sleepwalking, bedwetting, and night terrors, disturbances that are common in children, occur during slow-wave sleep, too. Night terrors are not nightmares but involve screaming and apparent terror, which are usually forgotten in the morning; they are not a sign of a disorder unless they continue beyond childhood. After Stage 4, the sleeper moves rather quickly back through the stages in reverse order. But rather than returning to Stage 1, the sleeper enters rapid eye movement sleep.

Rapid eye movement (REM) sleep is characterized by rapid horizontal movements of the eyes (under the closed lids) and a return to waking frequency EEG in the beta range. During REM sleep, respiration rate and heart rate increase, both males and females experience genital erection, and vaginal secretion increases in females. In spite of these signs of arousal, the person does not wake up; in fact, the sleeper is not easily aroused by noise but does respond to meaningful sounds, such as the sleeper's name. Another anomaly is that the body is very still—in fact, in a state of muscular paralysis or *atonia*. It is easy to see why some researchers call this stage *paradoxical sleep*, because *paradoxical* means "contradictory." Now we see evidence that the basic rest and activity cycle continues into sleep. A complete cycle through the stages of sleep—like the daydreaming cycle—takes about 90 minutes to complete. The night's sleep is a series of repetitions of this ultradian rhythm, although the length of REM sleep periods increases and the amount of slow-wave sleep decreases through the night (Figure 15.6).



Description

Figure 15.6 Time Spent in Various Sleep Stages During the Night.

As the night progresses, deep sleep decreases, and time in REM sleep (dark bars) increases.

If people sleeping in the laboratory are awakened by the researcher during REM sleep, about 80% of the time they report dreaming. Dreams also occur during other sleep stages, but they are less frequent, less vivid, and less hallucinatory. Even people who say that they do not dream report dreaming when they are awakened from REM sleep; they often describe their experience as "thinking" (H. B. Lewis, Goodenough, Shapiro, & Sleser, 1966). Apparently, "nondreamers" just fail to remember their dreams in the morning; in fact, we ordinarily remember a dream only if we wake up before the short-term memory of the dream has faded (Koulack & Goodenough, 1976). High-density EEG recording (using 256 channels) has revealed high-frequency activity (10–50 Hz) in areas related to the dream content—in the right posterior parietal cortex when the dream concerned a specific spatial setting, in Wernicke's area when speech was involved, and in the fusiform face area when people's faces were a part of the dream (Siclari et al., 2017).

The Functions of Sleep

The effects of sleep loss leave no doubt about the importance of sleep. You have seen, for example, that the early morning hours are particularly vulnerable times for traffic accidents and major disasters. Cognitive functioning suffers especially;

reducing sleep time to 6 hours or 4 hours for 14 days reduced alertness and working memory performance, with deficits equivalent to one night or two nights of total sleep deprivation, respectively (Van Dongen, Maislin, Mullington, & Dinges, 2003). Early research efforts were based on the idea that the main function of sleep is rest and restoration; the major focus was on **non-REM sleep**, which is characterized by decreased metabolic activity and slowed breathing and heart rate. One reason is that after total sleep deprivation, Stage 4 non-REM sleep is recovered before REM sleep (Anders & Roffwarg, 1973). Another reason is that slow-wave sleep increases following exercise; after athletes competed in a 92-kilometer race, slow-wave sleep was elevated for four consecutive nights (C. M. Shapiro, Bortz, Mitchell, Bartel, & Jooste, 1981). However, this effect appeared to be due to overheating; if runners on a treadmill were sprayed with water to cool them down, there was no change in slow-wave sleep (Horne & Moore, 1985). Heating only the head with a hair dryer was sufficient to increase slow-wave sleep later (Horne & Harley, 1989), which led Horne (1992), to suggest that slow-wave sleep promotes cerebral recovery from daily activities, especially in the prefrontal cortex.

? What are the functions of REM and slow-wave sleep?

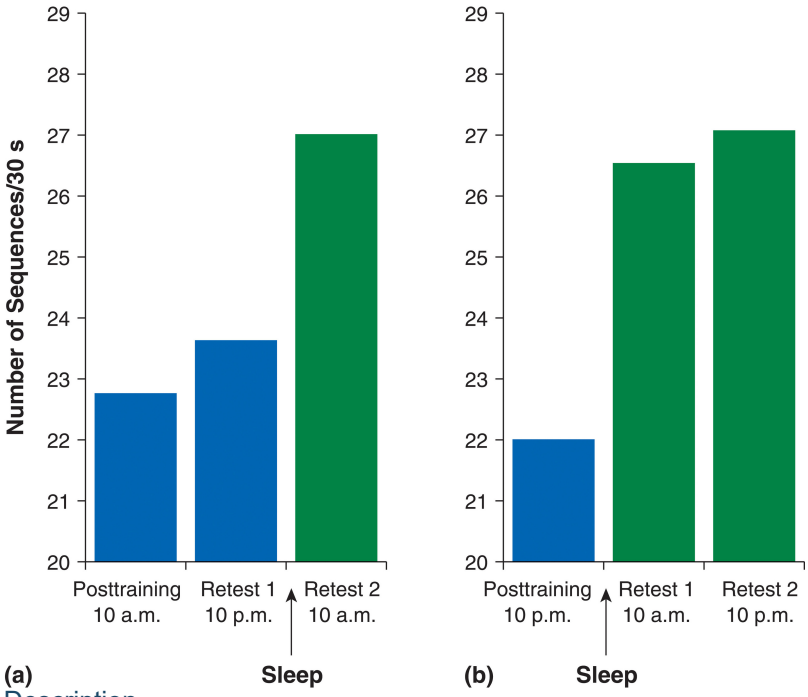
To find out what functions REM sleep serves, researchers deprived volunteers of REM sleep by waking the research participants every time EEG and eye movement recordings indicated that they were entering a REM period. When this was done, the subjects showed a “push” for more REM sleep. They went into REM more frequently as the study progressed and had to be awakened more often; then on uninterrupted recovery nights, they tended to make up the lost REM by increasing their REM from about 20% of total sleep time to 25% or 30% (Dement, 1960). To psychoanalytically oriented theorists, these results were evidence of a psychological need for dreaming, but because REM sleep is so pervasive among birds and mammals, most neuroscientists believe that any explanation must be a biological one, and they treat dreaming as merely the by-product of spontaneous neural activity in the brain.

One hypothesis is that REM sleep promotes neural development during childhood. Infant sleep starts with REM rather than non-REM sleep, and the proportion of sleep devoted to REM is around 50% during infancy and decreases through childhood until it reaches an adult level during adolescence (Roffwarg, Muzio, & Dement, 1966). According to this hypothesis, excitation that spreads through the brain from the pons during REM sleep encourages differentiation, maturation, and myelination in higher brain centers, similar to the way spontaneous waves of excitation sweep across the retina during development to help organize its structure (see Chapter 3). There is some evidence from studies of the immature visual systems of newborn cats that REM sleep, particularly these waves from the pons, regulates the rate of neural development (Shaffery, Roffwarg, Speciale, & Marks, 1999). The fact that sleep is associated with the upregulation of a number of genes involved in neural plasticity (see Chapter 12), as well as other genes that contribute to the synthesis and maintenance of myelin and cell membranes (Cirelli, Gutierrez, & Tononi, 2004), is certainly consistent with this neurodevelopmental hypothesis. In addition, it suggests our next topic, which deals with the role of sleep beyond the developmental period. In the words of Giulio Tononi and Chiara Cirelli (2014), sleep is “the price we pay for plasticity” (p. 12).

Sleep, Plasticity, and Memory

In Chapter 12, you learned that a period of sleep following learning enhances later performance (Figure 15.7). REM sleep has received the most attention; it increases during the sleep period following learning, and REM sleep deprivation after learning reduces retention (see review in Dujardin, Guerrien, & Leconte, 1990; Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994; C. Smith, 1995). How much REM sleep increases depends on how well the subject learned (Hennevin, Hars, Maho, & Bloch, 1995). Observation of hippocampal activity after learning suggests why REM sleep is important. Replay during REM sleep of the same neural activity that occurred during learning (see Chapter 12) is synchronized with spontaneous theta-frequency (4–7 Hz) activity in the hippocampus (Stickgold, Hobson, Fosse, & Fosse, 2001); in other words, the peaks of one wave coincide with the peaks of the other. After 4 to 7 days,

the time during which memories become independent of the hippocampus, the replay shifts out of phase with the theta activity, with the peaks of one wave coinciding with the troughs of the other. This suggests that a period of consolidation is followed by one of deleting connections—representing old memories, inaccurate connections, or both.

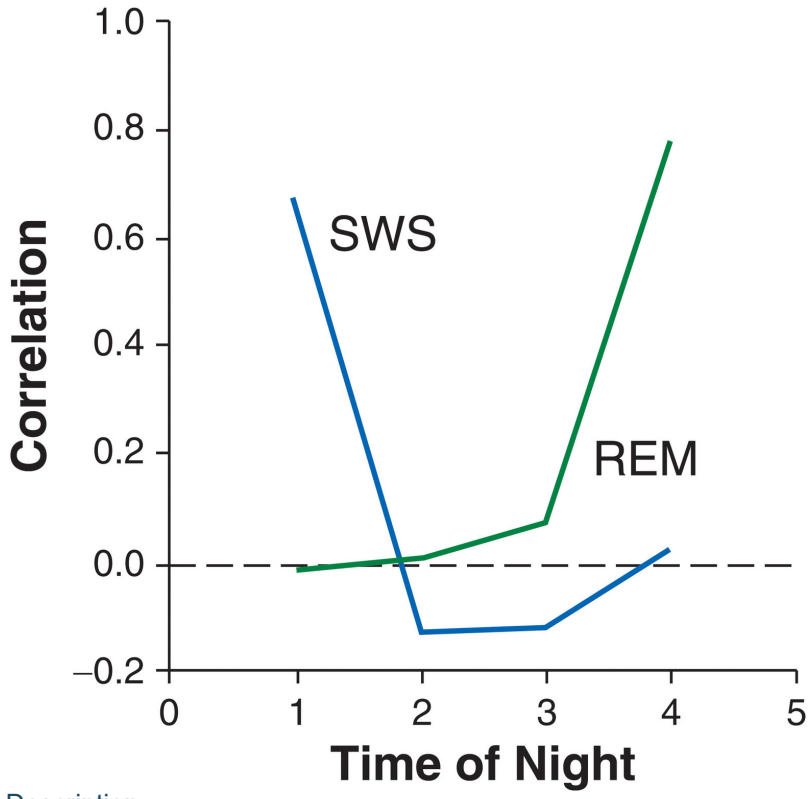


Description

Figure 15.7 Improvement in Learning Following Sleep.
Participants learned a motor skill task and were retested twice at 10-hour intervals. There was no statistically significant improvement for individuals who remained awake during the interval (a, Retest 1), but performance improved following sleep (a, Retest 2, and b, Retest 1 and Retest 2).

Source: Adapted from "Practice With Sleep Makes Perfect: Sleep-Dependent Motor Skill Learning," by M. P. Walker, T. Brakefield, A. Morgan, J. A. Hobson, and R. Stickgold, 2003, *Neuron*, *35*, pp. 205–211.

Some research suggests that consolidation is a multistep process requiring a combination of slow-wave and REM sleep. Overnight improvement on a visual discrimination task in humans was correlated with the percentage of slow-wave sleep during the first quarter of the night *and* the percentage of REM sleep in the last quarter of the night (Figure 15.8; Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000). "Driving" slow-wave activity by applying a 0.75-Hz oscillating current to the scalp or by pulsing a tone at the same rate as the naturally occurring slow-wave activity improved the recall of word associations learned prior to sleep (Papalambros et al., 2017; Westerberg et al., 2015).



Description

Figure 15.8 Correlation of Slow-Wave and REM Sleep With Overnight Task Improvement.
These graphs show the correlation of slow-wave sleep (SWS) and REM sleep with improvement on a visual discrimination task at the beginning of the next day's practice. They indicate that SWS has more effect during the first quarter of the night, whereas REM is important during the fourth quarter.

Source: Adapted with permission from Stickgold et al., "Sleep, Learning, and Dreams: Off-line Memory Reprocessing," *Science, 294,* pp. 1052–1057. © 2001 American Association for the Advancement of Science.

In their synaptic homeostasis hypothesis, Tononi and Cirelli (2013, 2014) argue that there is far better evidence for synaptic pruning during sleep than for consolidation; they believe this pruning improves the accuracy of information that was stored during waking by eliminating inaccurate connections. According to them, ripples, slow waves, and sleep spindles down-select synapses that were activated rarely during waking or that fit less well with old memories, whereas synapses that were strengthened repeatedly during waking or that are better integrated with older memories are protected. Luisa de Vivo and her colleagues (2017) used three-dimensional electron microscopy to confirm that, during sleep, synaptic spines decreased at smaller, less stable synapses, whereas stronger synapses were spared.

Evidence points to other maintenance going on during sleep as well. Using 3-D time-lapse imaging, Israeli researchers were able to observe single cells in the brains of live zebrafish, thanks to the fish's totally transparent bodies. They found that the chromosomes in neurons were more active during sleep, and that repair of damage to DNA accelerated during that time (Zada, Bronshtein, Lerer-Goldshtein, Garini, & Appelbaum, 2019). Another intriguing idea is that the brain cleanses itself of toxins during sleep. Researchers recently discovered a network of channels formed by glia (dubbed the "glymphatic system"), which transport cerebrospinal fluid among the brain cells. During sleep, extracellular spaces expand about 60%, allowing cerebrospinal fluid to mix with waste-containing interstitial fluid and flush the waste

out. Glymphatic activity is inhibited by norepinephrine during wakefulness and enhanced by norepinephrine suppression during non-REM sleep (Cordone, Annarumma, Rossini, & De Gennaro, 2019; Hauglund, Pavan, & Nedergaard, 2020). Injecting a colored dye into the brains of mice as they slept and a dye of another color when they woke up revealed that large amounts of CSF flows through the brain during sleep but not during the awake state. When the researchers injected β-amyloid proteins into the brains of the mice, the CSF cleared the proteins from the brain twice as fast during sleep (Xie et al., 2013). (Students note: This is one more argument for getting enough sleep!)

Brain Structures of Sleep and Waking

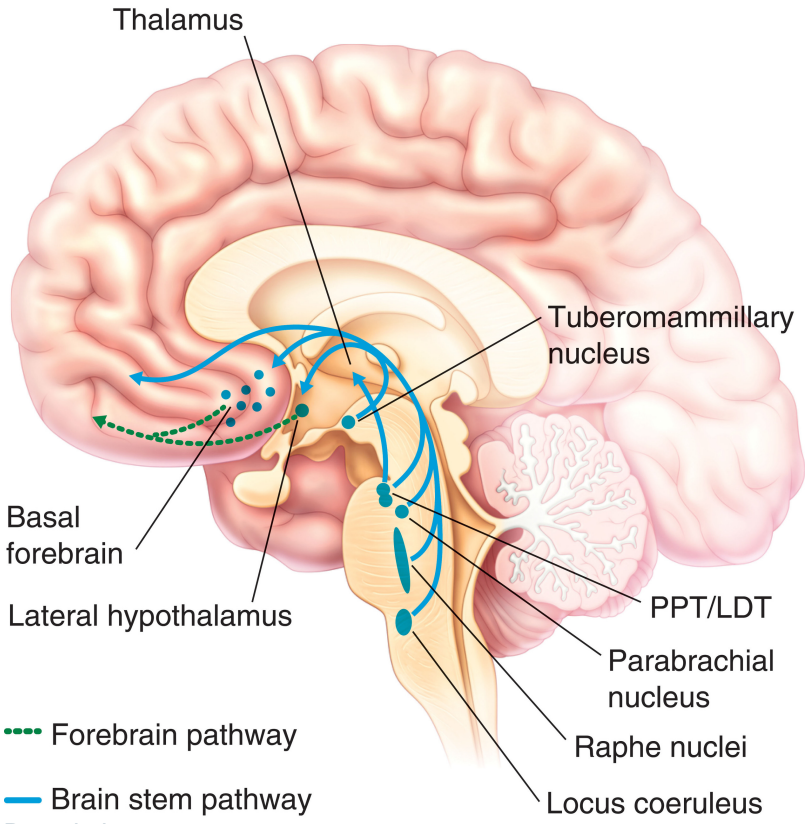
We have seen one of the ways sleep can be regarded as an active process: A great deal of activity goes on in the brain during sleep; in fact, the brain's energy use is not significantly lower in sleep than during waking and may even increase during slow-wave sleep (Dworak, McCarley, Kim, Kalinchuk, & Basheer, 2010). For the second aspect of this active process, we turn to the brain structures involved in turning sleep on and off. There is no single sleep center or waking center; sleep and waking depend on a variety of structures that integrate the timing of the SCN with homeostatic information about physical conditions such as fatigue, brain temperature, and time awake. Sleep is a homeostatic process, in that a period of deprivation is followed by a period of sleep; the balance between the two is brought about by mutually inhibiting wake and sleep centers. The network of structures governing sleep and waking is complex, so you will want to trace its connections carefully in the figures that accompany the following discussion. Except where noted, the following discussion is taken from the thorough review of the literature by Clifford Saper and his Harvard colleagues (Saper, Fuller, Pedersen, Lu, & Scammell, 2010). We will begin with the structures that produce wakefulness.

? What brain structures are responsible for sleep and waking?

Waking and Arousal Controls

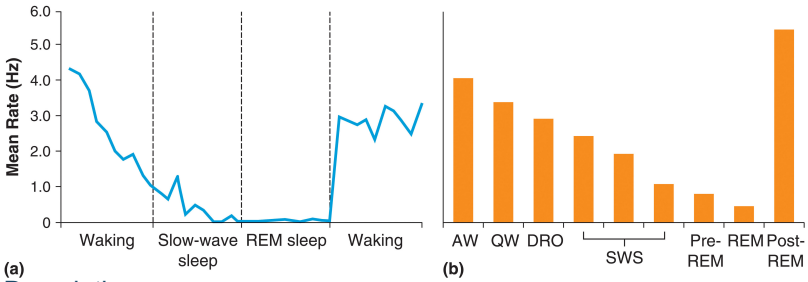
The waking network consists of two major pathways (Figure 15.9); we will start with the *brainstem arousal centers*, which send their activating signals to higher levels of the brain. This ascending pathway is itself made up of two branches. The first consists of *pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT)*, which fire most rapidly during wakefulness and REM sleep and most slowly during non-REM sleep, apparently driving the cortical activation seen outside non-REM sleep. The second branch includes the *locus coeruleus*, *raphe nuclei*, *tuberomammillary nucleus*, and *parabrachial nucleus*. Figure 15.10 shows how firing varies with sleep and waking in two of these areas. The brainstem branches send excitatory signals to the prefrontal cortex.

Figures Brought to Life



Description

Figure 15.9 Structures of Waking and Arousal.
Several interacting structures and pathways produce waking, maintain arousal during waking, and increase arousal during REM sleep.



Description

Figure 15.10 Firing Rates in Brain Stem Arousal Centers During Waking and Sleep.
(a) Activity in the locus coeruleus; (b) activity in the raphe nuclei. Note that these nuclei are most active during waking, relatively quiet during non-REM sleep, and (unlike the PPT/LDT) almost silent during REM sleep. (AW = alert waking; QW = quiet waking; DRO = drowsy; SWS = slow-wave sleep; pre-REM = 60 seconds before REM; post-REM = first second after REM ends.)

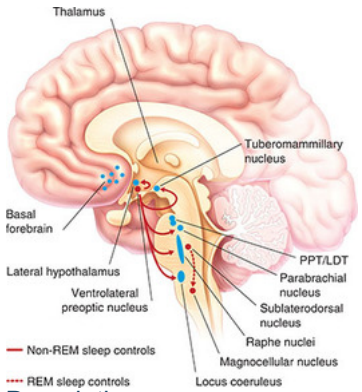
Sources: (a) Copyright 1981 by the Society for Neuroscience; (b) From "Activity of Serotonin-Containing Nucleus Centralis Superior (Raphe Medianus) Neurons in Freely Moving Cats," by M. E. Trulson et al., *Experimental Brain Research*, *54*, 33–44, fig. 2. © 1984.

Although lesions of these brain stem structures cause a loss of wakefulness, both animals and humans recover normal sleep-wake cycles within a period of weeks or months; this underscores the additional contribution of the *forebrain arousal centers*. The *basal forebrain* produces wakefulness and desynchronization of the EEG;

disabling animals' basal forebrains with an anesthetic causes them to fall into a deep, non-REM sleep. Similarly, orexin (hypocretin)-releasing neurons in the *lateral hypothalamus* both suppress REM sleep and sustain wakefulness. Like the brain stem centers, the forebrain arousal centers innervate the prefrontal cortex.

Non-REM Sleep Controls

The most important structure in the non-REM sleep network is the *ventrolateral preoptic nucleus (VLPO)* of the hypothalamus (Figure 15.11). Its neurons fire two to four times faster during non-REM sleep than during wakefulness and double that again as sleep deepens further. These neurons send inhibitory signals to the arousal network. Rats with lesions of the VLPO still sleep about 50% as much as normal rats, which means there must be other sleep centers inhibiting the arousal systems. At least one has been identified, the *parafacial zone* in the medulla (Anaclet et al., 2014).

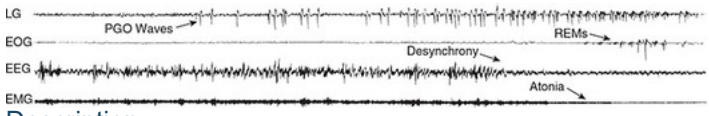


Description

Figure 15.11 Brain Mechanisms Regulating Sleep.
Sleep is brought about primarily by suppressing activity in arousal structures (shown in blue).

REM Sleep Controls

High-voltage **PGO waves**, so called because of their path of travel from the pons through the lateral geniculate nucleus of the thalamus to the occipital area, begin about 80 seconds before the start of a REM period and apparently are what initiate the EEG desynchrony of REM sleep (Figure 15.12; Mansari, Sakai, & Jouvet, 1989; Steriade, Paré, Bouhassira, Deschênes, & Oakson, 1989). PGO waves are as characteristic of REM sleep as rapid eye movements are, and their arousal of the occipital area may account for the visual imagery of dreaming. Firing in PPT/LDT nuclei becomes synchronized with PGO waves, while firing in the other arousal centers (locus coeruleus, raphe nucleus, and tuberomammillary nucleus) almost disappears. This suggests that the PPT/LDT might interact with the PGO nuclei to regulate alternation between non-REM and REM sleep.



Description

Figure 15.12 PGO Waves, EEG Desynchrony, and Muscle Atonia.
The records are of electrical activity in the lateral geniculate nucleus (LG), eye movements (EOG, electrooculogram), electroencephalogram (EEG), and muscle

tension (EMG, electromyogram). Notice that PGO waves signal the beginning of EEG desynchrony, rapid eye movements, and atonia several seconds later.

Source: Copyright 1989 by the Society for Neuroscience.

The most important REM sleep center in the pons is the *sublaterodorsal nucleus (SLD)*, which appears to govern switching in and out of REM sleep. Lesioning the SLD reduces REM sleep in rats; in cats, it eliminates output to the magnocellular nucleus in the medulla, which is responsible for the atonia of REM sleep. Lesioned cats seemed to be acting out their dreams (assuming that cats dream), and their movements often woke them up (Shouse & Siegel, 1992).

Sleep Disorders

Insomnia

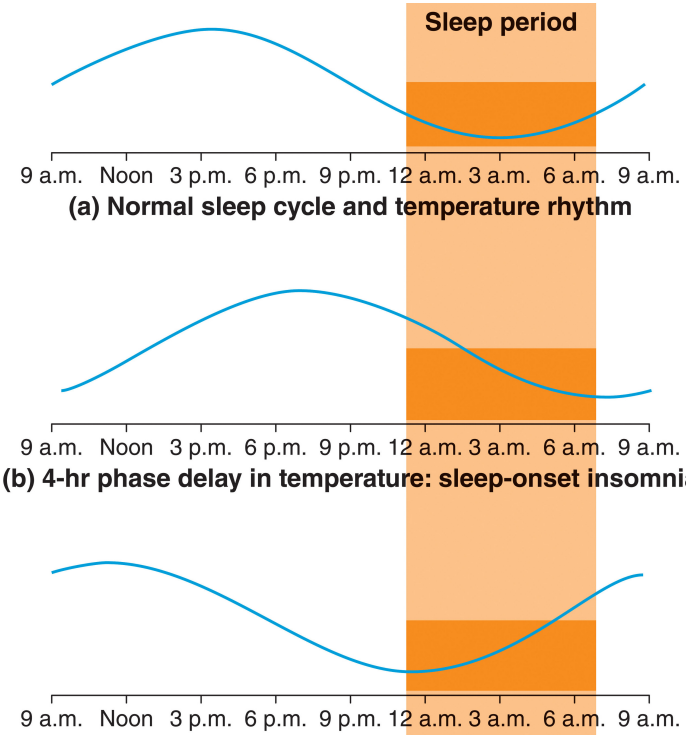
Insomnia is the inability to sleep or to obtain adequate-quality sleep, to the extent that the person feels inadequately rested. The failure to get enough sleep is part of the lifestyle of industrialized countries, but many people who try to get an adequate amount of sleep complain that they have difficulty either falling asleep or staying asleep. It is difficult to determine prevalence accurately because diagnosis is based on self report, but the data indicate that 20% to 35% of the population have some symptoms and that 10% to 20% suffer from clinically significant insomnia, with women affected significantly more often (Buysse et al., 2008). In a survey by the National Sleep Foundation (2002), more than half the respondents reported that they had trouble sleeping or woke up unrefreshed at least a few nights per week, and one third had experienced at least one symptom of insomnia every night or almost every night in the past year. There are several indications that the sleep quality of insomniacs suffers from hyperarousal. These include excess high-frequency EEG during non-REM sleep (Perlis, Smith, Andrews, Orff, & Giles, 2001) and disturbance of the hypothalamic-pituitary-adrenal axis (see Chapter 8), with increased secretion of cortisol and adrenocorticotropic hormone during the night (Vgontzas et al., 2001).

? What are the causes of sleep disorders?

Insomnia is important not only as a nuisance but also because sleep duration has important implications for health. A meta-analysis involving more than 5 million participants found that sleeping less than 5 or 6 hours per night is associated with increased mortality, hypertension, coronary and cardiovascular diseases, obesity, and diabetes (Itani, Jike, Watanabe, & Kaneita, 2017). We learned more recently that two gene mutations allow a very few people to sleep 6 hours and still feel rested (G. Shi et al., 2019). Whether the mutations also afford protection from diseases associated with short sleeping remains to be seen. A surprising finding in the meta-analysis was that long sleeping—for more than 9 hours per night—also is associated with increased mortality, as well as coronary and cardiovascular disease, stroke, obesity, and diabetes (Jike, Itani, Watanabe, Buysse, & Kaneita, 2018). In a study of 1.1 million men and women, sleeping more than 8.5 hours was associated with as great an increase in risk of death as sleeping less than 4.5 hours (Kripke, Garfinkel, Wingard, Klauber, & Marler, 2002). We have to be very careful about interpreting the causal relationship between sleep variations and health, however.

Insomnia can be brought on by a number of factors, such as stress and poor sleep hygiene (irregular sleep hours, screen time before bed). Insomnia can also occur as a rebound effect as a person attempts to reduce dependence on addictive sleep aids. Sleep disturbance often is associated with psychological disorders, particularly depression (D. J. Taylor, 2008). The association between insomnia and depression has a genetic basis, as does the link with diabetes (M. B. Stein et al., 2018). Loss of gray matter in the orbitofrontal cortex and the parietal cortex (Altena, Vrenken, Van Der Werf, van den Heuvel, & Van Someren, 2010) and reduced white matter integrity in the right hemisphere, thalamus, and corpus callosum (S. Li et al., 2016) could be unique to insomnia or associated with psychological disorders.

People with sleep difficulties often show a shift in their circadian rhythm. Irregular sleep habits can shift the rhythm, but there is good evidence for cause operating in the other direction, with poor entrainment disrupting sleep. Normally, people fall asleep when their body temperature is decreasing in the evening and wake up when it is rising. But if your body temperature is still high at bedtime (phase delay), you will experience sleep-onset insomnia; if your body temperature rises too early (phase advance), you will wake up long before the alarm clock goes off (Figure 15.13). Sleep is also more efficient if you go to bed when your body temperature is low; for example, a volunteer living in isolation from time cues averaged a 7.8-hour sleep length when he went to bed during his temperature minimum and a 14.4-hour sleep length when sleep began near his temperature peak (Czeisler, Weitzman, & Moore-Ede, 1980). Your *chronotype*—when your internal clock is synchronized to the 24-hour day—depends partly on your genes and partly on your environment (Roenneberg et al., 2004). People with advanced sleep phase disorder feel compelled to go to sleep around 7:30 in the evening and then wake up around 4:30 a.m. A mutation in the circadian clock gene *CKI* has been linked to the disorder (Y. Xu et al., 2005); more recently, three mutations in another clock gene, *PER2*, have also been identified (Chong, Ptáček, & Fu, 2012). Delayed sleep phase syndrome—late bedtime and rising—has been associated with the *PER3* clock gene (S. N. Archer et al., 2003).



Description

Figure 15.13 Effects of Disrupted Circadian Rhythm on Sleep.
Ordinarily, a person falls asleep while the body temperature is decreasing and awakens as it is rising (a). If body temperature is phase delayed (b), the person has trouble falling asleep; if body temperature is phase advanced (c), the person wakes up early. (Sleep period is the time in bed, whether the person is sleeping or not.)

It is usually easier for people to delay sleep at night than to rise early, which led to a treatment that seems completely counterintuitive. The patients had a 5- to 15-year history of sleep-onset insomnia so severe that they were not even going to bed until 4:15 a.m., on average. Rather than require them to retire earlier, the researchers had the patients *stay up 3 hours later* each day than the day before. After about a week of this routine—for example, going to bed at 8 a.m., 11 a.m., 2 p.m., 5 p.m., 8 p.m., and

11 p.m. on successive nights—their average sleep-onset time had shifted from 4:50 a.m. to 12:20 a.m., and their average waking time had shifted from 1:00 p.m. to 7:55 a.m. All five patients were able to give up the sleeping pills they had become dependent on, and improvement was long lasting (Czeisler et al., 1981). Phototherapy (see Chapter 14) is also sometimes used to reset the circadian clock.

Sleepwalking

Some of the sleep disorders are related to specific sleep stages. As we saw earlier, bedwetting, night terrors, and sleepwalking occur during slow-wave sleep. Although sleepwalking is most frequent during childhood, about 3% to 8% of adults sleepwalk (A. Dalton, 2005). Kenneth Parks's story in the opening vignette is not unique. The sleepwalking defense was first used in 1846 when Albert Tirrell was acquitted of the murder of his prostitute mistress and the arson of her brothel. Sleepwalking can be triggered by stress, alcohol, and sleep deprivation; Ken's jury was convinced that he was not responsible because he was sleep deprived due to stress over gambling debts and the loss of his job for embezzling; there was a personal and family history of sleepwalking, sleep talking, and bedwetting; and he produced a high level of slow-wave sleep during sleep monitoring (Broughton et al., 1994). His was the fourth and last sleepwalking murder case to end in acquittal; three subsequent defendants could not make a strong claim for nonresponsibility and were convicted (Lyon, 2009).

Sleepwalking increases with the degree of parental history for sleepwalking: 22% for children whose parents did not sleepwalk, 47% for children with one parent who sleepwalked, and 61% for children with two parents who sleepwalked (Petit et al., 2015). Not much is known about the genes involved, but people with a particular allele of the *HLA-DQB1* gene are 3.5 times as likely to sleepwalk as others (Lecendreux et al., 2003). The gene is a part of the immune system, and the authors suspect that cells important in sleep regulation have been attacked by the individual's immune system.

A less known non-REM sleep behavior is sexsomnia, engaging in sexual behavior while asleep. Although usually the worst consequence is embarrassment, the behavior has sometimes led to criminal charges (often leading to acquittal on grounds of nonresponsibility). The prevalence of sexsomnia is uncertain, but 11% of men and 4% of women seeking treatment for sleep disorders reported engaging in sexual behavior while asleep (American Academy of Sleep Medicine, 2010). Patients with sexsomnia didn't differ from the other patients in fatigue, depression, smoking, or caffeine consumption, but they were twice as likely to admit using illicit drugs.

Somewhere in between people who commit mayhem during sleepwalking and those who simply wander about the house are those who suffer from a *sleep-related eating disorder*, the subject of A Further Look.

A Further Look:

In the Still of the Night

Shirley Koecheler raids the refrigerator at night (N. Black & Robertson, 2010). She would like to quit because she's gaining weight, but she isn't aware she's doing it until she wakes up in the morning to a crumb-filled bed and an uncomfortably full stomach. She even had her husband hide the Easter candy, but the next morning, she found the wrappers from the chocolate bunnies in the wastebasket. Shirley's 24-year-old daughter Amy is also a sleep eater and has been since she was a toddler; the difference is that she doesn't gain weight. Anna Ryan, like Shirley, started sleep eating in adulthood; she didn't even know about the nighttime kitchen forays that added 60 pounds to her weight in a year and a half until she went to a sleep clinic to find out why she was exhausted every morning. Sleep eaters, usually women, ordinarily pass up healthy snacks for high-calorie junk food; they have also been known to eat soap, glue, frozen pizza, paper, and even eggshells (Epstein, 2010).

Source: © iStockphoto.com/Artfoliophoto

Sleep-related eating likely has multiple causes. In some instances, the individuals have other sleep disorders, such as sleep apnea, or a history of substance abuse. Some individuals who take pharmacological sleep aids (e.g., Ambien or benzodiazepines such as zolpidem) have reported drug-induced sleep-related eating, although the clinical features of these individuals seem to differ from those who have sleep-related eating as a primary diagnosis (Komada et al., 2016).

A reliable and effective treatment has not yet been found. Amy has responded well to a drug used to prevent seizures; she still sleep eats occasionally, but it's no longer the problem it once was. It took Anna and her doctor months of trial and error to find a combination of drugs that works, but now she sleeps through the night and is losing weight.

Narcolepsy

When stabilization of the sleep switch fails, the result is **narcolepsy**, a disorder in which individuals fall asleep suddenly during the daytime and go directly into REM sleep. Narcolepsy is often associated with **cataplexy**, in which the person has a sudden experience of one component of REM sleep, atonia, and falls to the floor paralyzed but fully awake. People with narcolepsy do not sleep more than others; rather, the boundaries are lost between sleep and waking (Nobili et al., 1996). Dogs also develop the disorder, and the study of canine narcolepsy has identified a mutated form of the gene that is responsible for the orexin receptor (Figure 15.14; L. Lin et al., 1999).

Figure 15.14 Cataplexy in a Dog.
Sleep researcher William Dement holds Tucker before (a) and during (b) an attack of cataplexy. Tucker is paralyzed but awake.

Source: Courtesy of Stanford University Center for Narcolepsy.

Almost all people with both narcolepsy and cataplexy have extremely low or even undetectable levels of orexin, due to a loss of orexin-secreting neurons in the hypothalamus (Higuchi et al., 2002; Kanbayashi et al., 2002). The neurons are destroyed by an autoimmune reaction; in some cases, this can be traced to an allele of a gene that encodes an immune receptor whose job is to detect foreign proteins (Hallmayer et al., 2009; Pedersen et al., 2019). Narcolepsy's concordance of 25% to 31% in identical twins (Mignot, 1998) leaves plenty of room for environmental influence. Again, the evidence points to an autoimmune disorder, with viruses as a trigger. Narcolepsy increases seven-fold following winter, when viruses are abundant, and it tripled above that following the 2009 H1N1 (swine flu) epidemic (F. Han et al., 2011).

REM Sleep Behavior Disorder

An apparent opposite of cataplexy is **REM sleep behavior disorder**; affected individuals are uncharacteristically physically active during REM sleep, often to the point of injuring themselves or their bed partners. A study of 93 patients, 87% of whom were male, found that 32% had injured themselves and 64% had assaulted their spouses (Olson, Boeve, & Silber, 2000). A 67-year-old man had tied himself to his bed with a rope at night for 6 years because he had a habit of leaping out of bed and landing on furniture or against the wall. One night, he was awakened by his wife's yelling because he was choking her; he was dreaming that he was wrestling a deer to the ground and was trying to break its neck (Schenck, Milner, Hurwitz, Bundlie, & Mahowald, 1989). Patients are more likely to smoke, drink heavily, have a mood disorder, and report a history of traumatic brain injury, welding work, and pesticide exposure. (Some of these may be a result of the disorder rather than a cause.) Within 10 years of diagnosis, about half of patients will have converted to Parkinson's disease, and many others follow later (Howell & Schenck, 2020). The link with Parkinson's is further confirmed by the presence of Lewy bodies in the brain. Lewy bodies are believed to begin in the medulla, where inhibition of the magnocellular nucleus ordinarily produces atonia; the Lewy bodies then progress upward through the brain before reaching the substantia nigra years later, when the full-blown disease appears (Braak et al., 2003).

Sleep as a Form of Consciousness

At the beginning of this discussion, we said that sleep is neither entirely conscious nor unconscious. Francis Crick (1994), who shared a Nobel Prize for the discovery of DNA's structure in 1962 before turning to neuroscience and the study of consciousness, believed that we are in a state of diminished consciousness during REM sleep and that we are unconscious during non-REM sleep. Certainly there are some elements of consciousness in the dream state, particularly in people who are *lucid dreamers*. You have probably had the occasional experience of realizing during a bad dream that it is not actually real and will end soon. That kind of experience is common for lucid dreamers—they are often aware during a dream that they are dreaming. People can be trained to become aware of their dreaming and to signal to the researcher when they are dreaming by pressing a handheld switch (Salamy, 1970). They can even learn to *control* the content of their dreams; they may decide before sleeping what they will dream about, or they may interact with characters in their dream (Gackenbach & Bosveld, 1989). This ability tells us that the sleeping person is not necessarily as detached from reality as we have thought. This point is further illustrated by sleepwalkers, who have driven cars, wandered the streets, brandished weapons (Schenck et al., 1989), and strangled, stabbed, and beaten people to death, all presumably during non-REM sleep.

? When you are asleep, are you unconscious?

So it is not clear where or whether the transition from consciousness to nonconsciousness occurs during sleep. The idea of a dividing line is blurred even further by reports that surgical patients can sometimes remember the surgical staff's conversations while they were anesthetized, and they show some memory later for verbal material presented at the time of surgery (Andrade, 1995; Bonebakker et al., 1996). Whether you draw the line of consciousness between waking and sleeping or between REM and non-REM sleep or between sleep and coma depends more on your definition of consciousness than on any clear-cut distinctions between these conditions. Perhaps it is better to think of sleep as a different state of consciousness along a continuum of consciousness. By identifying the various forms of consciousness and looking at what is going on in the brain, we can begin to get an idea of what consciousness really is.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

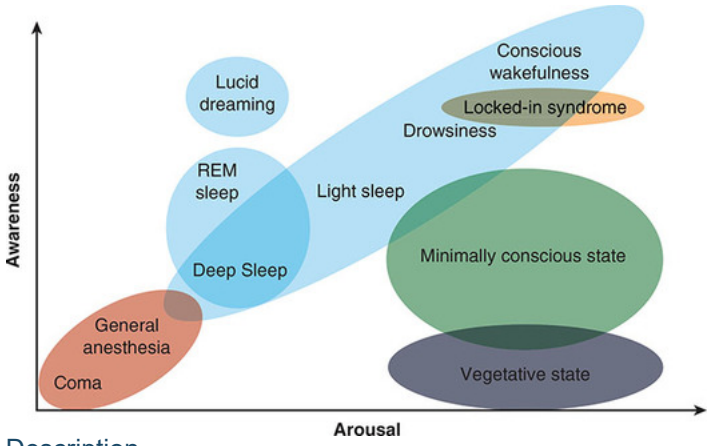
- Describe the circadian and ultradian rhythms discussed here.
- What, according to research, are the functions of REM and slow-wave sleep?
- Make a table showing the brain structures involved in sleep and waking, with their functions.
- Describe the sleep disorders and their causes.

THE NEURAL BASES OF CONSCIOUSNESS

Although strict behaviorists had banned consciousness as neither observable nor necessary for explaining behavior, over the last half of the 20th century, researchers began to find that various components of consciousness *were* necessary as they studied memory, attention, mental imagery, and emotion. Still, they carefully avoided using the word *consciousness* as they talked about awareness, attention, or cognition. Then, a few respected theorists began musing about consciousness in print and even suggesting that it was an appropriate subject for neuroscientists to study. Other scientists slowly began to come out of their closets, while their more cautious colleagues warned them not to allow consciousness to become a back door

for the reentry of the mind or for the proverbial homunculus, the “little man” inside the head who pulls all the levers. In the words of one team of writers, “consciousness is not some entity deep inside the brain that corresponds to the ‘self,’ some kernel of awareness that runs the show” (Nash, Park, & Willwerth, 1995).

So just what do we mean by *consciousness*? Actually, the term has a variety of connotations. We use it to refer to a state—a person is conscious or unconscious, and we use it in the sense of conscious experience, or awareness of something. *Consciousness* has additional meanings for researchers, though few try to define the term; Francis Crick (1994) suggested that any attempt at definition at this point in our knowledge would be misleading and would unduly restrict thinking about the subject. While agreeing on a definition is impractical, most researchers would likely be comfortable with the following assertions about consciousness. The person is aware, at least to some extent; as a part of awareness, the person holds some things in attention, while others recede into the background. Consciousness also involves memory, at least of the short-term variety, and fully conscious humans have a sense of self, which requires long-term memory. Consciousness varies in level, with coma and deep anesthesia on one extreme, alert wakefulness on the other, and sleep in between (see Figure 15.15). There are also altered states of consciousness, including hypnosis, trances, and meditative states. Over the next several pages, we will see how theorists have attempted to explain the neural bases of consciousness.



Description

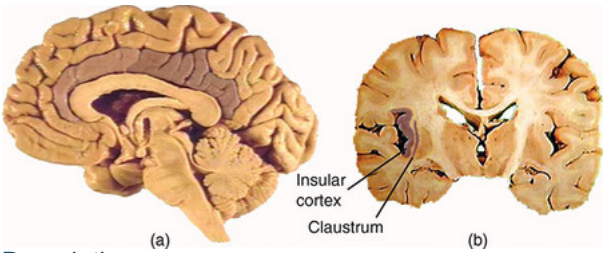
Figure 15.15 Awareness and Arousal in Normal and Impaired Consciousness.

Source: Adapted from “The Neural Correlate of (Un)awareness: Lessons From the Vegetative State,” by S. Laureys, 2005, *Trends in Cognitive Sciences*, *9*, pp. 556–559.

Structural and Network Explanations of Consciousness

One way researchers have sought the neural origins of consciousness is by identifying structures that alter consciousness, either through their normal functioning or as the result of stimulation or damage. We have long known that damage to the thalamus often results in loss of consciousness. Recently, researchers demonstrated that stimulating the central lateral thalamus in fully anesthetized monkeys restores wakefulness and normal neural processing; when the stimulation was turned off, the monkeys went back to sleep (Redinbaugh et al., 2020). In Chapter 8, we noted the role of the anterior insular cortex (AIC) in emotional awareness; lesions to the AIC impair emotional awareness and empathy, for example, for others’ pain (Figure 15.16; Gu, Hof, Friston, & Fan, 2013). The AIC and the anterior cingulate cortex (ACC) are part of the **salience network**, which detects significant stimuli that require attention. (We also mentioned in Chapter 14 that this network is abnormal in individuals with some OCD-related disorders.) The salience network switches back and forth between the default mode network, which you will remember is active when the brain is at wakeful rest, and the **central executive network**, which controls attention and working memory (Figure 15.17; Uddin, 2015). The claustrum is intriguing because of

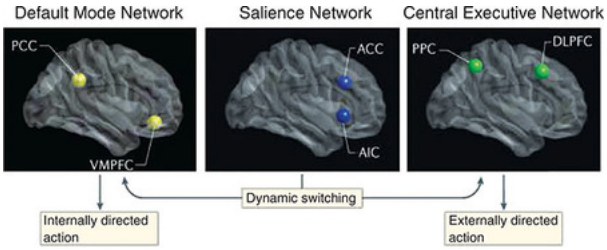
its unusually high density of connections with the primary sensory and motor areas and with the limbic system (refer to Figure 15.16 again; Torgerson, Irimia, Goh, & Van Horn, 2015). Both lesions and stimulation of the claustrum have been associated with loss of consciousness (Chau, Salazar, Krueger, Cristofori, & Grafman, 2015; Koubeissi, Bartolomei, Beltagy, & Picard, 2014); Van Horn (2019) suggests that it may synthesize sensory information and feed it into conscious experience.



Description

Figure 15.16 The Anterior Cingulate Cortex, Insular Cortex, and Claustrum. (a) The cingulate cortex (highlighted) is the gyrus overlying the corpus callosum; the anterior cingulate cortex is the area in a lighter color. (b) The insular cortex forms the inner wall of the lateral fissure; the claustrum is nearby, separated only by a narrow band of white matter.

Sources: (a) The University of Alabama at Birmingham Department of Pathology PEIR Digital Library© (http://peir.net). (color added to cingulate cortex). (b) Callisto Science: Retrieved from http://www.callisto-science.org/NSI/Neuroscience_Image_Database/Images/sol04139.jpg (background color removed; color added to insular cortex and claustrum).



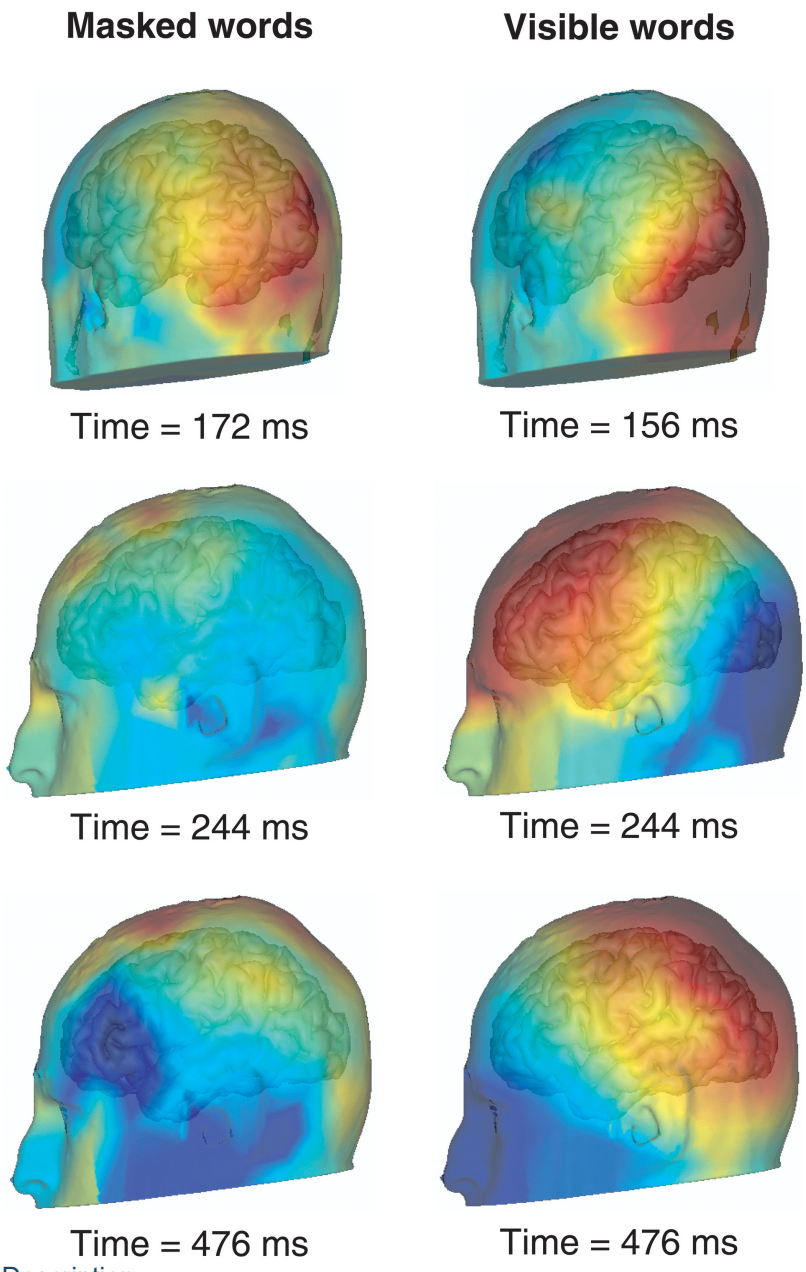
Description

Figure 15.17 The Default Mode, Salience, and Central Executive Networks. By detecting whether conditions require attention, the salience network switches back and forth between the internally directed default mode network and the task-oriented, externally directed central executive network. (ACC = anterior cingulate cortex; AIC = anterior insular cortex; DLPFC = dorsolateral prefrontal cortex; PCC = posterior cingulate cortex; PPC = posterior parietal cortex; VMPFC = ventromedial prefrontal cortex.)

Source: Uddin, L. O., (2015). Salience processing and insular cortical function and dysfunction. Nature Reviews Neuroscience, 16, 55–61. Copyright © Nature Publishing Group. Reprinted with permission.

Consciousness does not reside in these structures, of course; they exert their influence in cooperation with the rest of the brain; as a result, most research is focused on networks. For some, consciousness occurs when the activity of multiple widespread networks becomes synchronized, which enables them to share and integrate information (Baars, 2005; Dehaene & Naccache, 2001; Tononi, 2005). For example, when stimuli reach awareness, they produce widespread activity in the prefrontal and parietal cortex (Figure 15.18; reviewed in Baars, 2005; see Dehaene et al., 2001; Sergent, Baillet, & Dehaene, 2005). By contrast, during deep sleep, coma, vegetative states, epileptic loss of consciousness, and general anesthesia, coordinated activity among brain areas disappears and auditory and pain stimuli evoke activity limited to the primary areas. Many theorists believe that gamma frequency oscillations (> 30 Hz) between the thalamus and the cortex not only are the

most likely means of achieving this coordination but also are necessary for consciousness (Ribary, 2005). This is difficult to demonstrate, but human imaging shows that during anesthesia-induced loss of consciousness, functional connectivity is disrupted between the thalamus and the cortex, and activity decreases in the frontal-parietal network and in the default mode network (Akeju et al., 2014). In addition, 40-Hz or 100-Hz stimulation of the central thalamus in mice arouses them from sleep and produces widespread activation of the forebrain, and 10-Hz stimulation reduces brain activity and produces behavioral arrest (J. Liu et al., 2015). Network synchronization occurs at mid-range gamma frequencies when a person perceives a word or recognizes an image as a face; heightened attention results in synchronization at higher frequencies (Gallotto, Sack, Schuhmann, & de Graaf, 2017). These results are consistent with Giulio Tononi's (2008) hypothesis that consciousness depends on the brain's ability to integrate information, an ability that is impaired by diminishing connectivity.



Description

Figure 15.18 Map of Event-Related Potentials to Masked and Unmasked Visually Presented Words.
When briefly presented words were masked by following them with nonmeaningful visual stimuli, activation was largely confined to the primary visual area (as well as slightly delayed) and did not produce awareness. Unmasked words produced additional subsequent activity, which spread through the frontal and parietal cortex, accompanied by awareness.

Source: From "Cerebral Mechanisms of Word Masking and Unconscious Repetition Priming," by S. Dehaene et al., *Nature Neuroscience*, *4*, pp. 752–758, fig. 3, p. 755. © 2001 Macmillan Publishing. Used with permission.

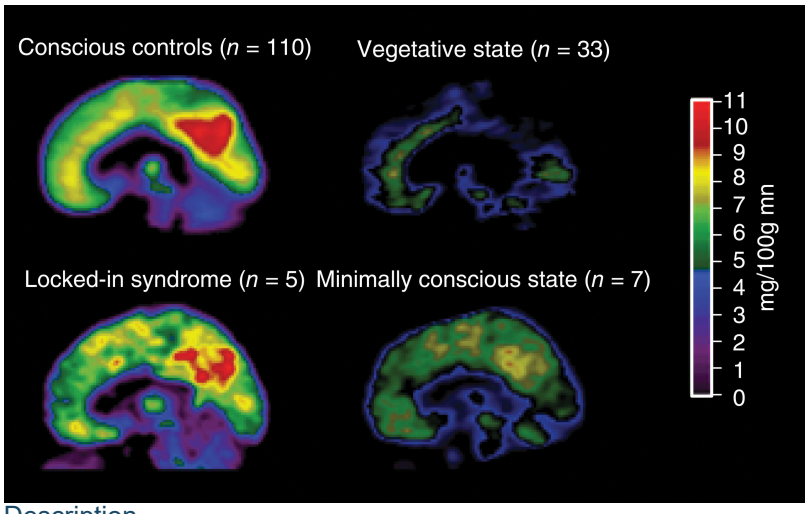
These issues are not purely academic; if you take A Further Look, you will see that a better understanding of consciousness is a practical necessity. Following that, we will tackle the three components of consciousness we mentioned earlier.

Awareness

As an abstract concept, awareness is difficult to define and more difficult to study. Researchers have typically adopted the shorthand definition that awareness is equivalent to the content of consciousness (Chau et al., 2015) and focused their attention on *awareness of something*. Taking this approach has helped identify brain areas as potential locations of awareness; although we have been able to associate the anterior insula with awareness of emotions, it has been easier to study awareness of objects, typically visual or spoken words. One strategy is to monitor the brain's activity in a scanner while flashing a series of words on a screen so briefly that they are at the threshold of detectability. If a person doesn't consciously notice the word, only the visual cortex is activated; as soon as the person becomes aware of the word, the lateral prefrontal cortex and posterior parietal cortex become active. These two areas and the thalamus have more interconnections with each other and the rest of the brain than any other region. These and other observations have led Daniel Bor and Ankil Seth to propose that the *prefrontal-parietal network* is important to awareness and to consciousness in general (Bor, 2013; Bor & Seth, 2012).

A Further Look:

Determining Consciousness When It Counts



Description

PET scans reveal metabolic activity corresponding to patients' level of consciousness.

Source: Reprinted from The Lancet, Vol.3, issue 9, S. Laureys, A. M. Owen, and N. D. Schiff, “Brain function in coma, vegetative state, and related disorders” p. 537-546, 2004 with permission from Elsevier.

One of the disturbing aspects of impaired consciousness is that it deprives patients of the ability to communicate with family and caregivers. The worst off are in a *coma* and completely unresponsive to stimulation. Those who are in a *vegetative state* respond reflexively to stimulation and cycle through wakefulness and sleep, but they do not interact voluntarily with their environment. The *minimally conscious* occasionally show voluntary responses, such as following visual movement or crying when they hear a family member’s voice, but they don’t reliably communicate. In contrast, patients with *locked-in syndrome* are fully conscious; however, they are paralyzed and are able to communicate only with eye movements or finger twitches, if at all.

Determining level of consciousness is critical not only for care decisions but also for developing ways of communicating with patients and restoring function. Patients classified as in a vegetative state were asked to imagine two different activities—hitting a tennis ball and navigating down a street or through their home; fMRI showed that five out of the six were able to produce distinctive activity in different regions of the brain (Monti et al., 2010). One of the patients, believed to be in a vegetative state for 5 years, was able to answer questions correctly by thinking about one of the activities for “yes” and the other activity for “no.” Even this limited communication would enable some patients to answer questions such as “Are you in pain?”

Physicians often rely on clinical observation for diagnosis rather than neurobehavioral testing. As a result, an estimated 40% of patients classified as being in a vegetative state are actually minimally conscious (Schnakers et al., 2009). PET scans and fMRI do a much better job (see figure), but they are expensive and not always available. J.-R. King and his associates (2013) developed a device that uses EEG to distinguish whether a series of beeps activates only the auditory area or a larger network, which would indicate some level of consciousness. In a preliminary test, the device distinguished among patients who were in a vegetative state, in a minimally conscious state, or fully conscious but locked in. An EEG monitoring system could also enable locked-in patients to communicate in complex sentences by focusing on letters one at a time on a keyboard display (Sellers, Ryan, & Hauser, 2014).

Detecting consciousness might also identify patients who could benefit from the therapies that are being developed. For example, both dopamine and GABA agonists have improved consciousness and communication in minimally conscious patients (Chatelle et al., 2014; L. R. D. Sanz et al., 2019). When a man who had been unreliably responsive for 6 years following brain injury received electrical stimulation of the thalamus, he was able to eat, watch movies, and communicate with gestures and phrases (Schiff et al., 2007). Because this therapy is highly invasive and typically provides only modest improvement to a minority of patients, researchers have pursued other alternatives. These include spinal cord stimulation and transcranial direct current stimulation (tDCS; see Chapter 4); both of these alter gamma-frequency activity and have shown initial promise in improving consciousness (Xia et al., 2018). A recent study showed that tDCS can be administered at home by caregivers. About 20% of patients who had been minimally conscious on average for 8 years showed modest improvement in consciousness (Martens et al., 2018). Caregivers reported the patients were more “present,” crying when they heard sad news or laughing at a funny scene on TV (H. Thomson, 2018).

What happens when part of this network is damaged? There are many possibilities, but the case of a man who often attributed one object’s color or direction of movement to another object after both parietal lobes were damaged is particularly instructive (L. J. Bernstein & Robertson, 1998). What this tells us is that brain damage impaired his ability to bind the spatial, color, and movement information together into awareness of the total object, in other words, an integrated percept. Increasingly, researchers are becoming convinced that binding involves synchronization of neural activity, typically in the gamma frequency range. Early studies found that during visual stimulation, 50% to 70% of neurons in the visual area of cats fired in synchrony at an average rate of 40 Hz (Engel, König, Kreiter, & Singer,

1991; Engel, Kreiter, König, & Singer, 1991). For an illustration of 40-Hz synchrony, see Figure 15.19. In response to a moving stimulus, activity synchronized between V1, the primary visual area, and V5, the area that detects movement (Engel, Kreiter, et al., 1991). This makes sense, because studies have indicated that visual awareness requires feedback to V1 from extrastriate areas such as V5 (reviewed in Tong, 2003). (You may want to refer to Figure 10.29 for the location of V1 and V5.)

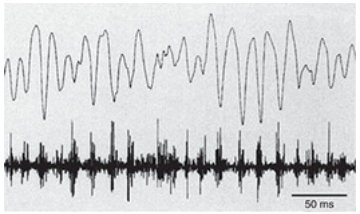
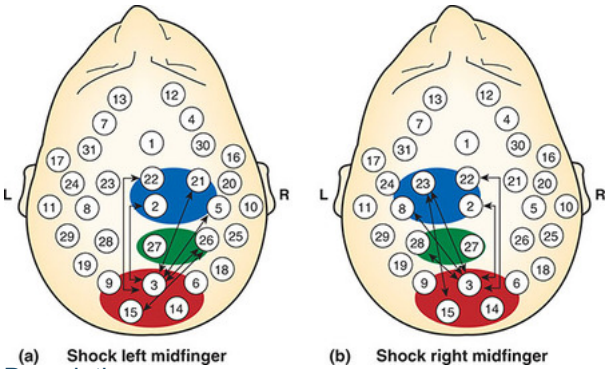


Figure 15.19 Forty-Hertz Oscillations in Neurons.
Top: Recording of the combined activity of all neurons in the vicinity of the electrode. Bottom: Activity recorded at the same time from two neurons adjacent to the electrode. By visually lining up the peaks and valleys of the two tracings, you can see that the two neurons are firing in synchrony with all the others in the area. (The upper tracing appears smoother because it is the sum of the activity of many neurons and because random activity is equally often positive and negative and cancels itself out.)

Source: Courtesy of Wolf Singer, Max-Planck-Institut für Hirnforschung.

? How does the brain solve the “binding problem”?

Later investigations revealed that activity is coordinated over much wider areas. For example, when researchers presented a light that had previously been paired with shock to the finger, activity became synchronized between the visual cortex and the finger area of the somatosensory cortex (Figure 15.20; Miltner, Braun, Arnold, Witte, & Taub, 1999). In a learning study, at the moment each subject became aware that one tone was associated with a visual stimulus and another was not, neural activity in the left prefrontal cortex became coordinated with activity in other parts of the brain, including the right prefrontal cortex, auditory association areas, visual cortex, and cerebellum (McIntosh, Rajah, & Lobaugh, 1999). Another study better illustrates the integrative nature of this synchrony. Words were presented in various colors and at various locations on a screen; whether the subject became aware of the word’s color or of its location—indicated by being able to recall it later—depended on whether activity increased in the frontal or temporal area. But if the individual registered both the color and the location, additional activity occurred in a part of the parietal cortex (Uncapher, Otten, & Rugg, 2006).



Description

Figure 15.20 Synchronized Activity Among Areas Involved in Learning.
Numbered circles indicate the location of EEG electrodes; colored areas, from anterior to posterior, are the primary somatosensory cortex, secondary somatosensory cortex, and visual cortex. A light was paired several times with a

shock to the middle finger. After that, presenting the light alone produced 40-Hz (average) EEG activity, which was synchronized between the visual cortex and the somatosensory cortex. The arrows indicate the pairs of electrodes between which synchrony was observed. Synchrony occurred (a) in the right hemisphere when shock had been applied to the left hand and (b) in the left hemisphere when shock had been applied to the right hand.

Source: Adapted from "Coherence of Gamma-Band EEG Activity as a Basis for Associative Learning," by W. H. Miltner et al., *Nature*, *397*, pp. 434–436. © 1999 Nature Publishing. Reprinted by permission.

Gaillard and his colleagues (2009) had the opportunity to record EEG activity from electrodes implanted in the brains of patients being evaluated for surgery to eliminate epileptic seizures; they recorded a cascade of awareness-defining events. Whether words reached awareness or not, they evoked gamma activity synchrony in the occipital area; if the words were recognized, about 300 milliseconds later, activity became synchronized among occipital, parietal, and temporal areas. In addition, neurons in one area appeared to be triggering the firing of neurons in the other areas.

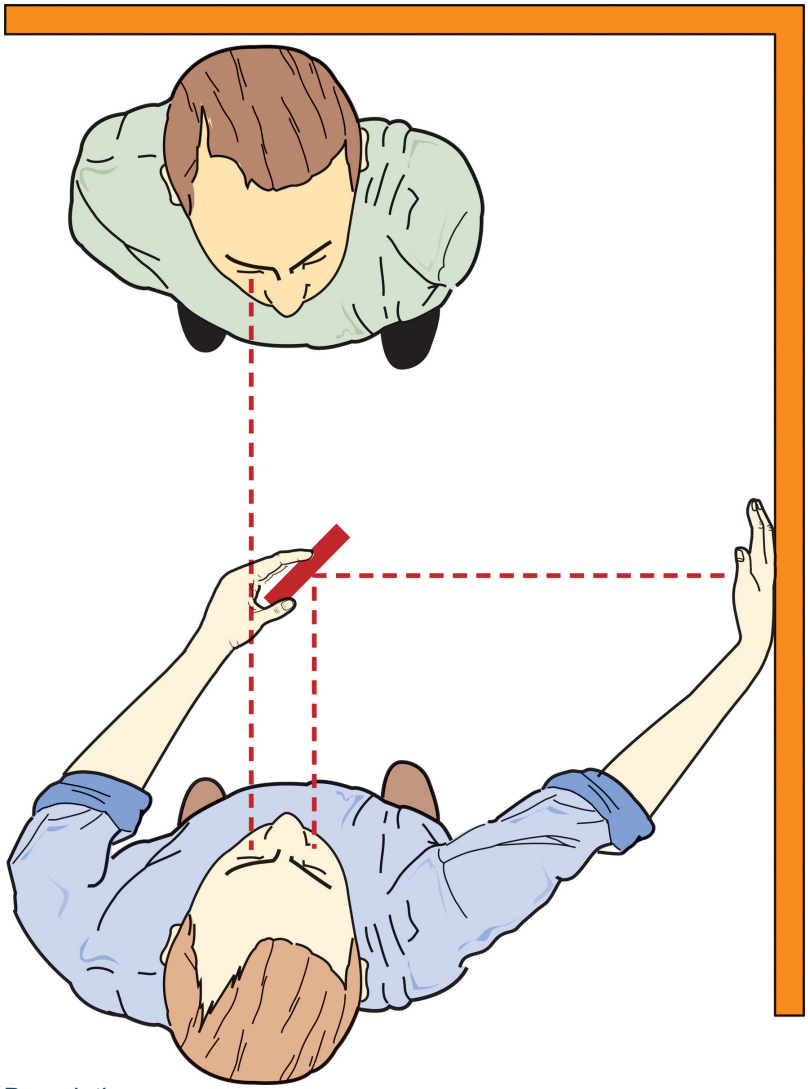
It is important to emphasize that much of our behavior is guided by processes that are outside awareness. A simple example would be our constant use of proprioceptive information to sit erect, to walk, and to reach accurately for objects in our environment. You learned in previous chapters that people with impaired facial recognition (prosopagnosics) are aroused by familiar faces that they do not otherwise recognize, that people with blindsight locate objects they deny seeing, and that patients with hippocampal damage improve over time on tasks that they deny having performed before. In one study, research participants were able to learn and use a pattern for predicting the location of a target on a computer screen, but not one of them was able to state what the pattern was—even when offered a reward of $100 for doing so. Through subtle training procedures, people have learned to associate a particular facial feature with a particular personality characteristic without being aware they had done so; in fact, when questioned, they did not believe that such a relationship existed (reviewed in Lewicki, Hill, & Czyzewska, 1992). We like to believe that our behavior is rational and guided by conscious decisions; perhaps we invent logical-sounding explanations for our behavior when we are not aware of its true origins. So what is the benefit of conscious awareness? This is actually a matter of debate, but one apparent advantage is that it enables a consistency in our behavior that would not be possible otherwise.

Attention

Separating attention and awareness is difficult, and it is even controversial whether we can do so. However, it is instructive to think of awareness as referring to the *content* of consciousness and attention as a *process*—the act of attending, or the act of selecting among the contenders for our awareness. **Attention** is the brain's means of allocating its limited resources by focusing on some neural inputs to the exclusion of others. It's hardly necessary to tell you how important attention is. When you are paying attention to a fascinating book, you may not notice all the hubbub around you. Some stimuli "grab" your attention, though; for example, the voice of a friend calling your name stands out above all the din. Also, what is attended to is easily remembered, and what escapes attention may be lost forever. The practical importance of attention is demonstrated in studies showing a four-fold increase in automobile accidents while drivers are using a cell phone (McEvoy et al., 2005; Redelmeier & Tibshirani, 1997). This is not due to the driver having one hand off the wheel, because the risk was just as high when the driver was using a speaker phone; clearly, the problem was attention.

Although you are aware of the importance of attention, you probably do not realize just how powerful it is. An interesting demonstration is the *Cheshire cat effect*, named after the cat in *Alice in Wonderland*, who would fade from sight until only his smile remained. Have a friend stand in front of you at arm's length while you hold a small mirror in your left hand so that it blocks your right eye's view of your friend's face but not the left eye's (Figure 15.21). Then hold your right hand so that you can see it in the mirror. (This works best if you and your friend stand in the corner of a room with

blank walls on two sides.) Your hand and your friend's face will appear to be in the same position, but your friend's face, or part of it, will disappear. If you hold your hand steady, you will begin to see your friend's face again, possibly through your "transparent" hand; move your hand slightly, and the face disappears again. By experimenting, you should be able to leave your friend with only a Cheshire cat smile. Your brain continues to receive information from both your hand and your friend's face throughout the demonstration; but because the two eyes are sending the brain conflicting information, telling it that two objects are in the same location, *binocular rivalry* occurs. The brain attends to one stimulus for a time and then switches to the other. Attention also switches when your hand or your friend's head moves and demands attention.



Description

Figure 15.21 Setup for Demonstrating the Cheshire Cat Effect.
Your view will alternate between your hand and your friend's face.

Attention is not just a concept; it is a physiological process, and changes in attention are accompanied by changes in neural activity. When an observer attends to an object, firing synchronizes between the brain areas involved, such as prefrontal with parietal neurons or parietal neurons with visual areas, depending on the task (Buschman & Miller, 2007; Saalmann, Pigarev, & Vidyasagar, 2007). When attention shifts, for example, during binocular rivalry, activity shifts from one group of neurons

in the visual cortex to another, even though the stimulus inputs do not change (Leopold & Logothetis, 1996). When research participants focused on an object's color, PET scans showed that activity increased in visual area V4; activation shifted to the inferior temporal cortex when they attended to the object's shape, and it changed to area V5 during attention to its movement (Chawla, Rees, & Friston, 1999; Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1990). We know that the shifts were due to attention, because activation also increased in V4 during attention to color, even when the stimuli were uncolored, and in V5 during attention to movement when the stimuli were stationary (Chawla et al., 1999).

? What is the neural basis of attention?

So our experience of attention is a reflection of changes in brain activity. The increases in cortical activity described here are at least partly due to the modulation of activity in the thalamus, which is the gateway for sensory information to the cortex (except for olfaction). The cortex can selectively inhibit thalamic neurons and determine which information will reach it (John, 2005). When human subjects attended to a stimulus, neural responses to that stimulus increased in the lateral geniculate nucleus of the thalamus, and responses to ignored stimuli decreased (O'Connor, Fukui, Pinsk, & Kastner, 2002). (Remember that you saw similar enhancement of sounds in Chapter 9.)

Attention involves a number of structures, and imaging suggests that they are organized into two networks: a dorsal one that allocates attention under goal-directed control and a ventral one that responds to stimulus demands (Asplund, Todd, Snyder, & Marois, 2010). However, the ACC may play an executive role (see Figure 15.16 again). In individuals studied just before receiving cingulate lesioning to treat their obsessive-compulsive disorder, 19% of ACC neurons either increased or decreased their firing rate during attention-demanding cognitive tests (K. D. Davis, Hutchison, Lozano, Tasker, & Dostrovsky, 2000). (You have to admire the brave souls who were willing to submit to mental arithmetic during brain surgery!) The ACC is also active during the Stroop word-color test, in which the participants must read color names as quickly as possible (Peterson et al., 1999). This is a difficult task, because some of the words are printed in a conflicting color; the researchers believe that the ACC modulates activity in attentional pathways to focus attention on the word's meaning and suppress attention to its color.

The Sense of Self

Consciousness is usually studied in relation to external reality, for example, object recognition or object awareness; this is in keeping with psychology's preference during much of its history for studying phenomena that are "out there," where we can observe them objectively. But an important aspect of consciousness is what we call the self; the sense of self includes an identity—what we refer to as "I"—and the sense of **agency**, the attribution of an action or effect to ourselves rather than to another person or external force.

? Where does our sense of self come from?

The sense of self is shared with few other species. We have learned this by using a cleverly simple technique developed for children. When the researcher puts a spot of rouge on a child's nose or forehead and places the child in front of a mirror, infants younger than about 15 months reach out and touch the "child in the mirror" or kiss it or hit it; older children will show self-recognition and use the mirror to examine the mysterious spot on their faces (M. Lewis & Brooks-Gunn, 1979). Chimpanzees are also able, after a time, to recognize themselves in the mirror; they examine the rouge spot, and they use the mirror to investigate parts of their body they have never seen before, such as their teeth and their behinds (Figure 15.22). Elephants, orangutans, porpoises, and—get this—magpies also recognize themselves, but monkeys do not (Gallup, 1983; Plotnik, de Waal, & Reiss, 2006; Prior, Schwarz, & Güntürkün, 2008; Reiss & Marino, 2001). Although monkeys learned how a mirror works and would turn to face a person whose reflection they saw in the mirror, after 17 years of continuous exposure to a mirror in their cage, they still treated their reflections like intruders

(Gallup & Povinelli, 1998). Stroke or the dementia of old age can impair mirror self-recognition in humans; the person may treat the mirror image as a companion, as an intruder who must be driven from the home, or as a stalker who appears in automobile and shop windows (T. E. Feinberg, 2001).

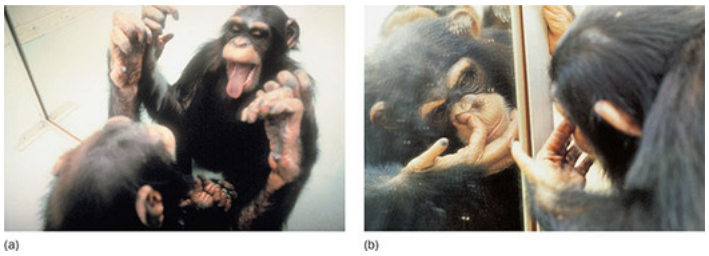


Figure 15.22 A Chimp Demonstrates Concept of Self.

Source: Gallup and Povinelli (1998). Photos courtesy of Cognitive Evolution Group, University of Louisiana at Lafayette.

Investigators have had some success in identifying neural correlates of the sense of self. Frontal-temporal damage, for example, impairs episodic memory and may produce a detachment from the self (M. A. Wheeler, Stuss, & Tulving, 1997). The ACC and the insula (see Figure 15.16) are important to sense of self and are active when people recognize their own faces, identify memories as their own, or recognize descriptions of themselves (Devue et al., 2007; Farrer et al., 2003; G. R. Fink et al., 1998). The medial parietal cortex is responsible for self-related memory, while self-evaluation engages the medial prefrontal cortex (Lou, Changeux, & Rosenstand, 2016). Transcranial magnetic stimulation (TMS) applied over the parietal area reduced participants' ability to recall words they had used to describe themselves compared to the words they had used to describe their best friend (Lou, Luber, Stanford, & Lisanby, 2010). TMS over the prefrontal cortex reduced or even reversed their tendency to describe themselves more positively than their best friend (Luber, Lou, Keenan, & Lisanby, 2012).

Farrer and Frith and their colleagues suggest that the sense of agency is mediated by the anterior insula and the angular gyrus, which is in the inferior parietal area (Farrer et al., 2003; Farrer & Frith, 2002). When research participants believed that they were controlling movements of a cursor or a virtual hand on a computer screen, activity increased in both insulas; when it became obvious that the experimenter was controlling the movement, activity shifted to the angular gyrus (Figure 15.23). In other research, activity increased in the inferior parietal cortex as the discrepancy increased between the person's movements and feedback from the movements; according to Farrer and her colleagues (2008), the angular gyrus contributes to the sense of agency by detecting discrepancies between actions and consequences. Later work found that a sense of agency occurred during a task when the inferior parietal cortex initiated gamma-frequency communication with frontal cortical areas (Ritterband-Rosenbaum, Nielsen, & Christensen, 2014). Interestingly, people with schizophrenia who believe their behavior is controlled by another person or agent show heightened parietal activity compared with other schizophrenia patients and controls (Spence et al., 1997).

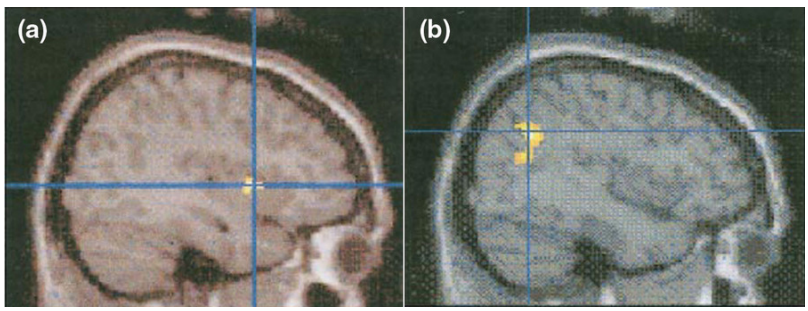


Figure 15.23 Brain Areas Involved in the Sense of Agency.
Attributing an effect (movement of a computer cursor) to oneself activated the insula (a); attributing the movement to another person activated the angular gyrus in the inferior parietal cortex (b).

Source: From "Experiencing Oneself vs. Another Person as Being the Cause of an Action: The Neural Correlates of the Experience of Agency," by C. Farrer et al., *NeuroImage*, *15*, pp. 596–603, fig. 2 and fig. 3, p. 598. © 2002 with permission from Elsevier, Ltd.

We do not find in these studies, nor should we expect to find, a brain location for the self; instead, what we see is scattered bits and pieces. We should regard the self as a concept, not an entity, and the sense of self as an amalgamation of several kinds of information, mediated by networks made up of many brain areas. Body image, memory, and the activity of mirror neurons are among the contributors to the sense of self; we will examine these topics and then consider two disorders of the self.

Body Image

Body image contributes to a sense of self because we have an identification with our body and with its parts; it is *our* body, *our* hand, *our* leg. A good example of the importance of body image to the sense of self is the phantom limb phenomenon. You learned in Chapter 11 that most amputees have the illusion that their missing arm or leg is still there (Figure 15.24). The illusion occurs in 80% of amputees and may persist for the rest of the person's life, which attests to the power of the body image. Distortions in the phantom sometimes add credibility to this point: One man was unable to sleep on his back because his phantom arm was bent behind him, and another had to turn sideways when walking through a door because his phantom arm was extended to the side (Melzack, 1992). Researchers once thought that phantoms occurred only after a person developed a *learned* body image, but we now know that phantoms can occur in young children and even in people born with a missing limb. The body image appears to emerge from the cortical homunculus (see Chapter 3), more than from experience, so it becomes a part of the self even when the image conflicts with reality.

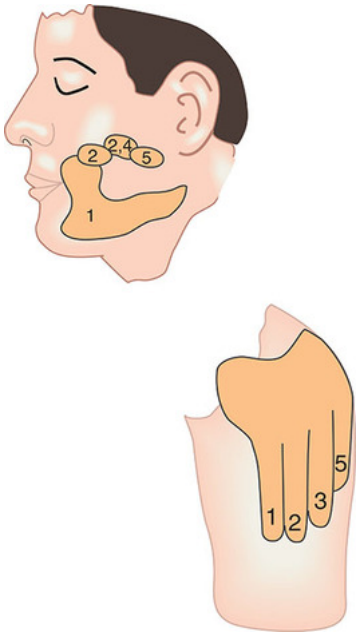


Figure 15.24 Maps of a Patient's Phantom Hand.
Touching the arm above the stump produced sensations of the missing hand. The same thing happened on the face, confirming what we saw in Chapter 11, that neurons from the face have invaded the hand area in the somatosensory cortex.

Source: Figure 2.2 from *Phantoms in the Brain* by V. S. Ramachandran, MD, PhD, and Sandra Blakeslee. Copyright © 1998 by V. S. Ramachandran and Sandra Blakeslee. Reprinted by permission of HarperCollins Publishers, Inc.

The “replacement” of a limb by a phantom does not prevent a feeling of loss, which can extend to the sense of self. This point was illustrated very graphically by S. Weir Mitchell, a Civil War physician who saw numerous amputees and presented some of his observations in the fictionalized account “The Case of George Dedlow” (S. W. Mitchell, 1866). Mitchell’s hero, who has lost both arms and both legs in battle, says,

> I found to my horror that at times I was less conscious of myself, of my own existence, than used to be the case…. I felt like asking someone constantly if I were really George Dedlow or not. (p. 8)

In Chapter 11, we saw an example of a more extensive loss in the case of Christina. Watching a home movie of herself from before the disease had destroyed her proprioceptive sense, she exclaimed,

> Yes, of course, that’s me! But I can’t identify with that graceful girl any more! She’s gone, I can’t remember her, I can’t even imagine her. It’s like something’s been scooped right out of me, right at the centre. (O. Sacks, 1990, p. 51)

Although information about the body is processed in the somatosensory cortex, body image is a phenomenon that develops primarily in adjacent parietal areas. An example comes from earlier attempts to eliminate phantoms by surgery; lesions in the somatosensory area had no effect, but lesioning the right posterior parietal cortex did suppress the sensations (Berlucchi & Aglioti, 1997). One of the functions of the insula is the integration of internal with external information; damage to the posterior part of the insula, which is located in the inferior parietal cortex, can produce a variety of symptoms, including denial that a paralyzed limb belongs to the patient or perception of an extra limb (Berlucchi & Aglioti, 1997; Karnath & Baier, 2010). In Chapter 11, we saw that damage to the inferior parietal area can also cause the most extreme of body image illusions, the out-of-body experience (Blanke & Arzy, 2005).

Memory

Without long-term memory, it is doubtful there can be a self, because there is no past and no sense of who the person is. In the words of the memory researcher James McGaugh, memory “is what makes us us” (A. Wilson, 1998). Loss of short-term memory is not as disruptive; patients such as H. M. (described in Chapter 12) have a lifetime of information about their past and about themselves as a background for interpreting current experience, even if they do not remember events that have occurred since their brain damage. However, for Alzheimer’s and Korsakoff patients, memory loss extends back several years before the onset of illness, as well as after the onset. Oliver Sacks’s patient Jimmie had lost 40 years of memories to Korsakoff syndrome; restless, unable to say whether he was miserable or happy, he reported that he had not felt alive for a very long time (O. Sacks, 1990).

Mary Frances, whom you met in Chapter 12, took another approach, explaining her situation with one false scenario after another. Another confabulator was the amnesia patient Mr. Thompson, who took an unauthorized day’s liberty from the hospital. At the end of the day, the cabdriver told the staff that he had never had so fascinating a passenger: “He seemed to have been everywhere, done everything, met everyone. I could hardly believe so much was possible in a single life” (O. Sacks, 1990, p. 110).

According to Sacks, Mr. Thompson had to “make himself (and his world) up every moment” by turning everyone on the ward into characters in his make-believe world and weaving story after story as he attempted to create both a past and a present for himself.

The confabulated stories amnesiacs tell can usually be traced back to fragments of actual experiences. This is consistent with the hypothesis introduced in our earlier discussion, that confabulation is a failure to suppress irrelevant memories due to damage in the frontal area (Benson et al., 1996; Schnider, 2003). But, like Mr. Thompson, confabulators often prefer an embellished past to an ordinary one (Fotopoulou, Solms, & Turnbull, 2004); this together with the involvement of the ACC (Turner, Cipolotti, Yousry, & Shallice, 2008) makes one suspect that the confabulation is also serving the self-image. The motivated nature of confabulation suggests the importance of real or imagined memories to the person’s identity. As the movie director Luis Buñuel (1983) said as he contemplated his own failing memory,

> You have to begin to lose your memory, if only in bits and pieces, to realize that memory is what makes our lives. Life without memory is no life at all…. Our memory is our coherence, our reason, our feeling, even our action. Without it, we are nothing.

Self, Theory of Mind, and Mirror Neurons

A sense of self requires the distinction between our self and other selves and, arguably, some understanding of other selves. We saw in the discussion of autism that an ability to attribute mental states to others is called theory of mind and that researchers who study mirror neurons believe they are critical to our development of that comprehension (see Chapter 13). They give mirror neurons considerable credit for social understanding (Gallese & Goldman, 1998), empathy (Gazzola, Aziz-Zadeh, & Keysers, 2006), and the ability to understand the intentions of others (Iacoboni et al., 2005). When volunteers watched a video clip, their mirror neurons responded more as a model reached for a full cup beside a plate of snacks (implying the intent to eat) than when the model reached for an empty cup beside an empty plate (implying the intent to clean up). The two scenes without the model produced no differences (Figure 15.25; Iacoboni et al., 2005).

Description

Figure 15.25 Different Intentions Distinguished by Mirror Neurons.
The implied intention of the actor in the photo on the left is to drink; in the photo on the right, it is to clean up. Different neurons were active as research participants viewed these two scenes, suggesting that mirror neurons can distinguish among intentions.

Source: From “Grasping the Intentions of Others With One’s Own Mirror Neuron System,” by M. Iacoboni, 2005, *PLoS Biology*, *3,* pp. 529–535, fig. 1 upper right and lower right, p. 530. Used under the Creative Commons Attribution (CC BY) license.

Malfunction in the mirror neuron system is one reason suggested for the failure of an individual with autism to develop a distinction between self and others, along with empathy and theory of mind (Cascio, Foss-Feig, Burnette, Heacock, & Cosby, 2012; J. H. G. Williams, 2008). Children with autism spectrum disorder took twice as long as control subjects to develop the rubber hand illusion, and the delay was correlated negatively with an empathy measure (Cascio et al., 2012). Justin Williams and his associates suggest that the problem is not in the mirror neurons themselves but in the regulation of their function by the ACC (J. H. G. Williams, Whiten, Suddendorf, & Perrett, 2001).

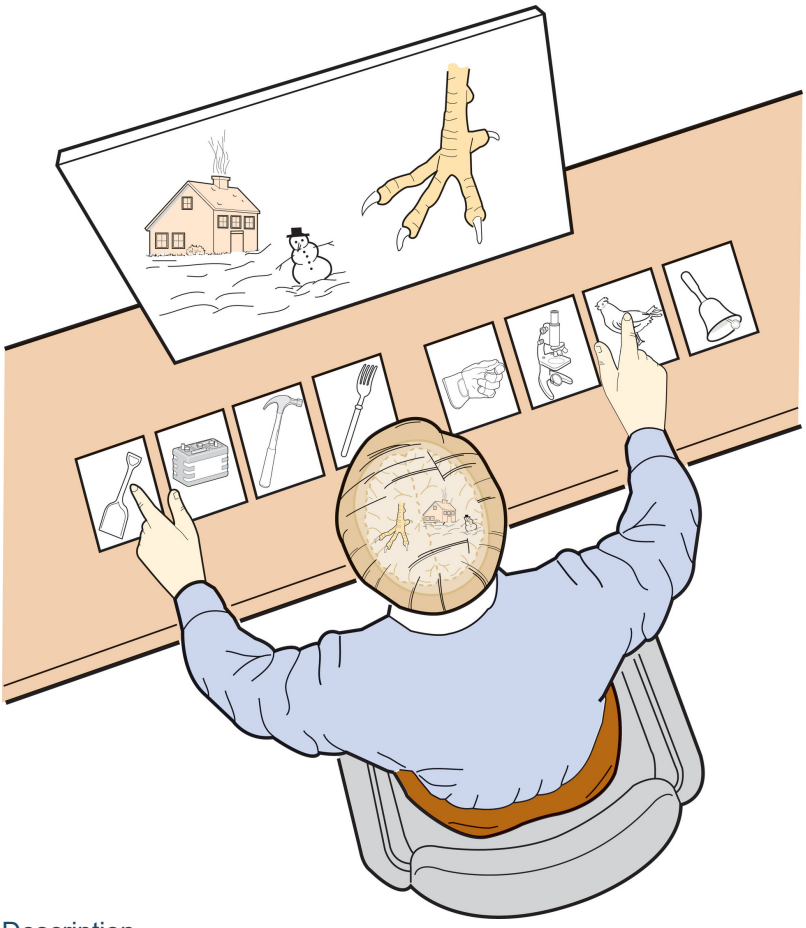
Split Brains and Dissociative Identity Disorder: Disorders of Self

Chapter 3 describes a surgical procedure that separates the two cerebral hemispheres by cutting the corpus callosum. This surgery is used to prevent severe epileptic seizures from crossing the midline and engulfing the other side of the brain. Besides providing a unique opportunity to study the differing roles of the two hemispheres, split-brain patients also raise important questions about consciousness and the self. Gazzaniga (1970) described a patient who would sometimes find his hands behaving in direct conflict with each other—for instance, one pulling up his pants while the other tried to remove them. Once the man shook his wife violently with his left hand (controlled by the more emotional right hemisphere), while his right hand tried to restrain the left. If the person with a severed corpus callosum is asked to use the right hand to form a specified design with colored blocks, performance is poor because the left hemisphere is not very good at spatial tasks; sometimes the left hand, controlled by the more spatially capable right hemisphere, joins in to set the misplaced blocks aright and has to be restrained by the experimenter.

? What do these disorders of self tell us?

Different researchers interpret these studies in different ways. At one extreme are those who believe that the major or language-dominant hemisphere is the arbiter of consciousness and that the minor hemisphere functions as an automaton, a nonconscious machine. At the other extreme are the researchers who believe that each hemisphere is capable of consciousness and that severing the corpus callosum divides consciousness into two selves. Sixty years of research have prompted most theorists to take positions somewhere along the continuum between those extremes.

Gazzaniga, for instance, points to the right hemisphere's differing abilities, such as the inability to form inferences, as evidence that the right hemisphere has only primitive consciousness (Gazzaniga, Ivry, & Mangun, 1998). He says the left hemisphere not only has language and inferential capability but also contains a module that he calls the "brain interpreter." The role of the **brain interpreter** is to integrate all the cognitive processes going on simultaneously in other modules of the brain. Gazzaniga was led to this notion by observing the split-brain patient P. S. performing one of the research tasks. P. S. was presented a snow scene in the left visual field and a picture of a chicken's foot in the right and asked to point to a picture that was related to what he had just seen. With the right hand, he pointed to the picture of a chicken, and with the left he selected a picture of a shovel (Figure 15.26). When asked to explain his choices, he (his left hemisphere) said that the chicken went with the foot and the shovel was needed to clean out the chicken shed. Unaware that the right hemisphere had viewed a snow scene, the left hemisphere gave a reasonable but inaccurate explanation for the left hand's choice. Although the right hemisphere has less verbal capability than the left, it can respond to simple commands; if the command "Walk" is presented to the right hemisphere, the person will get up and start to walk away. When asked where he or she is going, the patient will say something like "I'm going to get a Coke." According to Gazzaniga, these confabulations are examples of the brain interpreter making sense of its inputs, even though it lacks complete information.



Description

Figure 15.26 Split-Brain Patient Engaged in the Task Described in the Text.
His verbal explanation of his right hand's selection was accurate, but his explanation of his left hand's choice was pure confabulation.

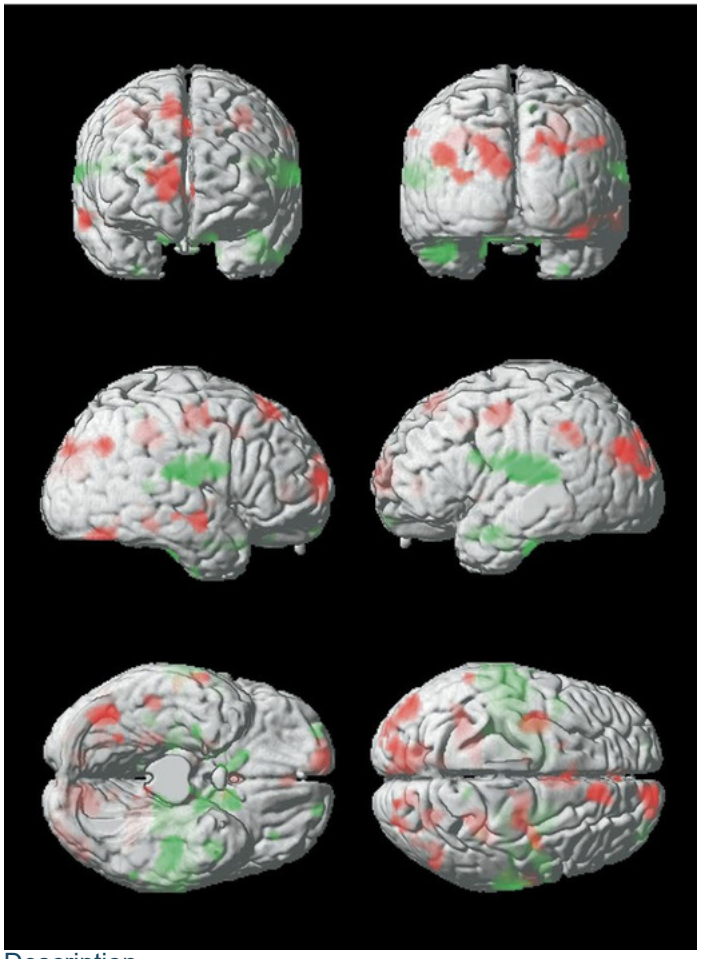
Illustration © 1998 John W. Karapelou, All Rights Reserved.

Perhaps researchers who view the right hemisphere's consciousness as primitive are confusing consciousness with the ability to verbalize the contents of consciousness. Assigning different levels of consciousness to the two hemispheres may be premature when our understanding of consciousness is itself so primitive. Research with split-brain patients tells us to avoid oversimplifying such a complex issue.

Another disorder of self is **dissociative identity disorder (DID**; formerly known as multiple personality), which involves shifts in consciousness and behavior that appear to be distinct personalities or selves. You may be familiar with this disorder from the movie *The Three Faces of Eve*. Shy and reserved, Eve White would have blackouts while her alter ego, Eve Black, spent the night on the town dancing and drinking with strange men. The puritanical Eve White would have to deal with the hangover, explain a closetful of expensive clothes she didn't remember buying, and sometimes fend off an amorous stranger she found herself with in a bar (Lancaster, 1958; Thigpen & Cleckley, 1957). Eve, whose real name was Chris Sizemore, went on to develop 22 different identities before she recovered. DID is listed as a diagnostic category in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM*-5; American Psychiatric Association, 2013), with a prevalence at 1.5% of American adults. However, a dramatic increase in total diagnosed cases from 500 in 1979 to 5,000 in 1985 (B. G. Braun, 1985) led to questions about the legitimacy of the disorder. The inflated numbers were attributed to overdiagnosis by therapists and to

fabrication by patients, who were motivated to please their therapist, to explain their troublesome behavior to themselves, or in some cases to avoid criminal prosecution.

Clinical diagnosis of DID is unreliable, which has led researchers to turn to neuroanatomy for evidence whether the disorder exists. They found reductions in both white matter and gray matter throughout much of the brain; the gray matter losses included the ACC and the insular cortex, which we mentioned earlier as important to the sense of self (Chalavi, Vissia, Giesen, Nijenhuis, Draijer, Barker, & Reinders, 2015; Reinders et al., 2018; Reinders et al., 2019). Simone Reinders and her colleagues (2006) looked for objective evidence for different identities in brain functioning. According to them, a DID patient has a "neutral identity," which copes with life by inhibiting memories of a traumatic past, and at least one "traumatic identity," which has access to those memories and responds to them. Figure 15.27 shows that patients' brains responded differently to a script recounting their traumatic memories when they were in the two different identity states.



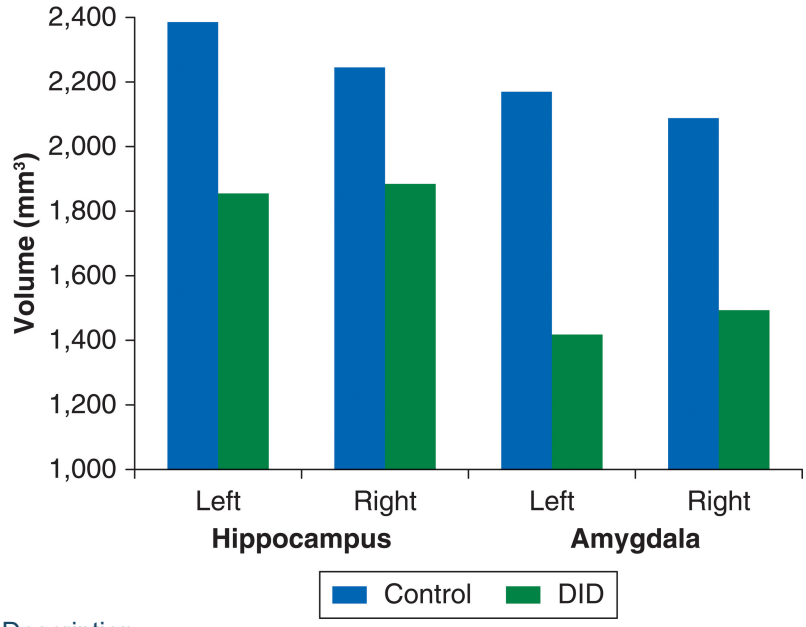
Description

Figure 15.27 Brain Responses of DID Patients to Traumatic Memories During Different Identity States.
Green areas indicate areas of greater blood flow while listening to a traumatic memory script during the traumatic identity state, compared to listening during the neutral identity state. Red areas are those where blood flow was greater while listening to the script during the neutral identity state, compared to the traumatic state.

Source: Reinders, A. A., Nijenhuis, E. R., Quak, J., Korf, J., Haaksma, J., Paans, A. M., et al. (2006). Psychobiological characteristics of dissociative identity disorder: A symptom provocation study.

Biological Psychiatry, 60, 730–740. Copyright © 2006 Society of Biological Psychiatry. Published by Elsevier Inc. All rights reserved.

The researchers chose traumatic memories as their way of evoking brain responses because it is virtually impossible to find a DID patient without a history of childhood onset posttraumatic stress disorder (PTSD). In fact, many researchers and psychiatrists consider DID to be a severe form of PTSD (Blihar, Delgado, Buryak, Gonzalez, & Waechter, 2020). Consistent with that view, numerous studies have found PTSD-typical decreases in hippocampal volume in DID patients (Figure 15.28; Chalavi, Vissia, Giesen, Nijenhuis, Draijer, Barker, & Reinders, 2015; Chalavi, Vissia, Giesen, Nijenhuis, Draijer, Cole, et al., 2015). Volume was reduced in both hippocampi in DID patients, while in PTSD-only patients, only the right hippocampus was affected. Note that the figure shows that amygdala size was also greatly decreased. It is widely believed that DID patients create new identities as a defense against continuing emotional stress; the low amygdala volume is consistent with the idea that this tactic represents a breakdown in fear handling (Şar, Dorahy, & Krüger, 2017).



Description

Figure 15.28 Hippocampus and Amygdala Size in Dissociative Identity Disorder. The hippocampi were 19% smaller and the amygdalas were 32% smaller in people with DID compared to control individuals.

Source: Based on Vermetten, E., Schmahl, C., Lindner, S., Loewenstein, R. J., & Bremner, J. D. (2006). Hippocampal and amygdalar volumes in dissociative identity disorder. American Journal of Psychiatry, 163, 630–636.

Concept Check

Take a Minute to Check Your Knowledge and Understanding

- Summarize the “coordination” explanation for consciousness described here.
- What four changes in the brain accompany shifts of attention?
- What roles do body image and memory play in the sense of self?

- What do “split-brain” studies tell us about consciousness?
- What brain differences have been found in patients with dissociative identity disorder?

IN PERSPECTIVE

There was a time when the topic of sleep was totally mysterious and dreaming was the province of poets and shamans. Now sleep and dreaming are both yielding to the scrutiny of neuroscience. Although we are still unclear about the functions of sleep, we are learning how various structures in the brain turn it off and on and how our body dances not only to a daily rhythm but also to another that repeats itself 16 times per day and controls our fluctuations in alertness, daydreaming, and night dreaming.

Consciousness is also giving up its secrets as researchers bring modern technologies to bear on awareness, attention, and memory. In other words, what was once a taboo topic is becoming accessible to the research strategies of science and is providing a whole new arena of opportunities to observe the brain at work.

In this final chapter, we have explored a unique field of research. The study of sleep has demonstrated neuroscience’s ability to unravel mysteries and dispel superstition. The investigation of consciousness has been more daring, taking scientists where none had gone before. That is the job of science, to push back darkness, whether by finding a treatment for depression or by explaining humanity’s most unique characteristics and capabilities. But we have traveled a road filled with questions and uncertain facts, and the schizophrenia researcher’s remark from 50 years ago that “almost everything remains to be done” still seems appropriate today (Heston, 1970, p. 254). If all this ambiguity has left you with a vaguely unsatisfied feeling, that is good; you may have the makings of a neuroscientist. And we have left the most exciting discoveries for you.

Chapter Summary

Sleep and Dreaming

- Circadian rhythms are rhythms that repeat on a daily basis, affecting the timing of sleep and several bodily processes. The suprachiasmatic nucleus is the most important control center but not the only one. The rhythm is primarily entrained to light.
- Several ultradian rhythms occur within the day. One involves alternating periods of arousal during waking and stages that vary in arousal during sleep.
- REM sleep is when most dreaming occurs, but it has also been implicated in neural development and learning.
- Slow-wave sleep may restore cerebral and cognitive functioning; it participates in learning and memory, possibly in the form of both consolidation and pruning. It also appears to be a period of waste removal.
- Waking, sleep, and sleep's stages are controlled by separate, complex networks of brain structures.
- Insomnia, sleepwalking, narcolepsy, and REM sleep behavior disorder represent the effects of psychological disturbances in some cases and malfunction of the sleep-wake mechanisms in others.
- Sleep is an active period, a state of consciousness that is neither entirely conscious nor unconscious.

The Neural Bases of Consciousness

- Any very specific definition of consciousness is premature, but normal consciousness includes awareness, attention, and a sense of self.
- How awareness comes about is unclear, but research has shown that it involves the thalamus, anterior cingulate cortex, insula, claustrum, and coordinated activity in brainwide networks.
- Attention allocates the brain's resources, actually shifting neural activity among neurons or brain locations.
- Body image, memory, and mirror neurons are important contributors to a sense of self.
- Split-brain surgery provides an interesting research window into consciousness, which has prompted debates about each hemisphere's contribution to consciousness and to the self.
- Dissociative identity disorder involves adoption of multiple identities, possibly as a reaction to severe trauma. There are reports that DID is associated with brain anomalies.

Study Resources

For Further Thought

- Animals cycle on a 24-hour schedule, either sleeping at night and being active during the day or vice versa. An alternative would be to sleep when fatigue overtakes the body, regardless of the time. What advantages can you think of for a regular schedule?

- Machines and, probably, some simpler animals function just fine without awareness. Awareness places a significant demand on neural resources. What adaptive benefits do you see?

- Do you think we will be able to understand consciousness at the neural level? Why or why not? Will computers and robots achieve consciousness?

Test Your Understanding

1. Discuss the functions of sleep, including the REM and slow-wave stages of sleep.
2. Discuss attention as a neural phenomenon.
3. Discuss the function of confabulation in the behavior of split-brain patients and Korsakoff patients.

Select the best answer:

1. The most important function of sleep is
    1. restoration of the body.
    2. restoration of the brain.
    3. safety.
    4. a, b, and c
    5. uncertain.
2. The body's own rhythm, when the person is isolated from light, is
    1. approximately 24 hours long.
    2. approximately 25 hours long.
    3. approximately 28 hours long.
    4. unclear because of conflicting studies.
3. Jim is totally blind, but he follows a 24-hour day-night cycle like the rest of us and seems comfortably adapted to it. Studies suggest that he relies on
    1. a built-in rhythm in his SCN.
    2. nonvisual receptors in his eyes.
    3. clocks and social activity.
    4. a and b
    5. b and c
4. According to most neuroscientists, dreams are
    1. a way of resolving the day's problems.
    2. a replay of daytime learning.
    3. symbolic representations of emotional material.
    4. a by-product of neural activity.
5. Evidence that REM sleep specifically enhances consolidation is that
    1. REM increases after learning.
    2. REM deprivation interferes with learning.
    3. performance improves following REM sleep.
    4. a and b
    5. a, b, and c
6. An "executive" sleep and waking center is located in the
    1. rostral pons.
    2. lateral hypothalamus.
    3. preoptic area of the hypothalamus.
    4. magnocellular nucleus.
    5. None of the above
7. The magnocellular nucleus is responsible for
    1. initiating sleep.
    2. waking the individual.
    3. switching between REM and non-REM sleep.
    4. producing atonia during REM.

8. Cataplexy is
    1. sleep without a REM component.
    2. a waking experience of atonia.
    3. a more severe form of narcolepsy.
    4. clinically significant insomnia.
9. Evidence supporting a network theory of consciousness is
    1. the broader effect of a sensory stimulus during consciousness.
    2. that an executive for the networks has been identified.
    3. that there are several centers of consciousness.
    4. None of these
10. Neuroscientists generally agree that binding of spatial, color, and movement information into a single percept involves
    1. the insula.
    2. the anterior cingulate cortex.
    3. synchronization of neural activity between brain areas.
    4. activation of the default mode network.
11. An EEG of 40 Hz is associated with
    1. binding.
    2. dreaming.
    3. consolidation.
    4. attention.
12. The part of the brain where attention is shifted among stimuli may be the
    1. basal forebrain.
    2. magnocellular nucleus.
    3. thalamus.
    4. raphe nuclei.
13. An explanation offered for confabulation links it to damage to the
    1. locus coeruleus.
    2. temporal lobes.
    3. pulvinar.
    4. frontal areas.
14. Some evidence for the credibility of dissociative identity disorder is
    1. the high frequency of its diagnosis.
    2. different patterns of physiological measures.
    3. patients' lack of incentive to fake the symptoms.
    4. location of damage in one brain area.

Answers:

1. e, 2. d, 3. b, 4. d, 5. e, 6. e, 7. d, 8. b, 9. a, 10. c, 11. a, 12. c, 13. d, 14. b.

For Further Reading

1. *Sleep Disorders for Dummies*, by Max Hirshkowitz and Patricia Smith (Wiley, 2004), is a guide for anyone who has trouble sleeping.
2. *Self Comes to Mind: Constructing the Conscious Brain*, by Antonio Damasio (Random House, 2010), discusses the brain bases of consciousness.
3. "The Source of Consciousness," by Ken Paller and Satoru Suzuki (*Trends in Cognitive Sciences*, 2014, *18*, 387–389), explains why we should be optimistic about discovering the bases of consciousness and why the research should be funded.
4. "What's the Point of Consciousness?" by Bob Holmes (*New Scientist*, May 13, 2017, 28–31), explores whether animals might be conscious and the evolution and function of consciousness.
5. "Forty-Five Years of Split-Brain Research and Still Going Strong," by Michael Gazzaniga (*Nature Reviews Neuroscience*, 2005, *6*, 653–659), is a useful and extensive summary of what we have learned from the research.
6. "The Patient's Journey: Living With Locked-In Syndrome," by Nick Chisholm and Grant Gillett (*British Medical Journal*, 2005, *331*, 94–97), is Nick's account of his partial recovery from locked-in syndrome, a disorder that leaves the patient completely conscious but unresponsive, unable to vocalize, open the eyes, or signal to doctors that he or she is fully aware. The article contains useful details

about the disorder and the problem of distinguishing it from a persistent vegetative state.
7. “Whose Body Is It, Anyway?” by Graham Lawton (*New Scientist*, March 21, 2009, 36–37), tells you how to create the illusion that you have three hands and how to get a glimpse of what an out-of-body experience is like.

Key Terms

agency 530

attention 528

brain interpreter 534

cataplexy 521

central executive network 524

dissociative identity disorder (DID) 535

insomnia 518

melatonin 509

narcolepsy 521

non-REM sleep 513

PGO waves 517

rapid eye movement (REM) sleep 512

REM sleep behavior disorder 521

salience network 524

slow-wave sleep 511

suprachiasmatic nucleus (SCN) 508

ultradian rhythm 511

Descriptions of Images and Figures

Back to Figure

Each bar shows an illustration of the corresponding animal. The data from the graph are tabulated below.

Back to Figure

1. The scan shows the following labels: Thalamus, corpus callosum, cerebral cortex, basal ganglia, and suprachiasmatic nucleus, indicated by an arrow. The nucleus is depicted by a dark.
2. The suprachiasmatic nucleus is depicted by a bright region.

Back to Figure

The data from the illustration are tabulated below.

Back to Figure

The horizontal axis is labeled Time since sleep onset, and ranges from 00:00 to 7:00 in hourly increments. The vertical axis is labeled sleep stage, and lists stage 4, stage 3, stage 2, stage 1, and awake. All data are approximate. The transition through sleep stages are as follows. Sleep onset is at midnight, and the transition is to stage 4 just before 1:00, to stage 2 just before 2: 00, to stage 4 at 2:30, to stage 1 just after 3:00, to stage 3 at 4:00, to stage 1 at 5:00, to stage 3 at 5:30, to stage 1 at 6:00, and to stage 2 at 6:30. REM sleep occurs in stage 1, just before 2, just after 3, between 4:30 and 5:00, and between 6:00 and 6:30.
Back to Figure

In both graphs, the vertical axis is labeled number of sequences per 30 seconds, and ranges from 20 to 29 in increments of 1.

a. The approximate data from the graph are tabulated below.

Sleep was between retest 1 and retest 2.

b. The approximate data from the graph are tabulated below.

Sleep was between posttraining and retest 1.

Back to Figure

The horizontal axis is labeled Time of night, and ranges from 0 to 5 in increments of 1. The vertical axis is labeled Correlation, and ranges from negative 0.2 to 1.0 in increments of 0.2. The approximate data from the graph are tabulated below.

Back to Figure

The brain stem pathway is from locus coeruleus, raphe nuclei, parabrachial nucleus, P P T/L D T, and tuberomammillary nucleus to lateral hypothalamus and basal forebrain, and toward the forebrain. The forebrain pathway is from lateral hypothalamus and basal forebrain toward the forebrain.

Back to Figure

In both graphs, the vertical axis is labeled mean rate in hertz, and ranges from 0 to 6.0 in increments of 1.0. All data are approximate.

1. The mean rate decreases from 4.2 hertz to 1.0 hertz during waking, decreases to 0 hertz during slow-wave sleep, remains at 0 hertz during REM sleep, increases sharply to 3.0 hertz during waking, and continues increasing gradually.
2. The data from the graph are tabulated below.

Back to Figure

The pathway of non-REM sleep control is from the ventrolateral preoptic nucleus to the lateral hypothalamus and to tuberomammillary nucleus, P P T/L D T, parabrachial nucleus, Raphe nucleus, and locus coeruleus along the brain stem. The pathway of REM sleep control is from sublaterodorsal nucleus to magnocellular nucleus. Both nuclei are in the brain stem.

Back to Figure

Initially, L G shows low frequency low voltage waves, E O G is flat, E E G shows high frequency high voltage waves, and E M G shows high frequency low voltage waves. Few seconds after the occurrence of sharp, P G O waves in L G, E O G shows irregular waves corresponding to REMs, the voltage of E E G decreases indicating desynchrony, and the voltage of E M G becomes zero, indicating atonia.

Back to Figure

In all graphs, the sleep period is between 11 p.m. and 7 a.m.

1. Normal sleep cycle temperature rhythm: The body temperature peaks at 3 p.m., reaches a minimum at 3 a.m., and rises.
2. 4-hour phase delay in temperature, Sleep-onset insomnia: The body temperature peaks at 7 p.m. and reaches a minimum at 7 a.m.
3. 4-hour phase advance in temperature, Sleep-termination insomnia: The body temperature peaks at noon, reaches a minimum at 12 a.m., and rises.

Back to Figure

The horizontal axis is labeled arousal, and the vertical axis is labeled awareness. The data from the graph are as follows.

- Coma and general anesthesia: Very low arousal and very low awareness.
- Lucid dreaming: Low arousal and high awareness.
- REM sleep: Low arousal and moderate awareness.
- Deep sleep: Low arousal and low awareness.
- Light sleep: Moderate arousal and moderate awareness.
- Drowsiness: High arousal and high awareness.
- Conscious wakefulness: Very high arousal and very high awareness.
- Locked-in syndrome: Very high arousal and high awareness.
- Minimally conscious state: Very high arousal and low awareness.
- Vegetative state: Very high arousal and very low awareness.

Coma and general anesthesia are grouped together and deep sleep, light sleep, drowsiness, and conscious wakefulness are grouped together.

Back to Figure

1. Sagittal view shows cingulate gyrus located superior to anterior cingulate cortex in corpus callosum.
2. Coronal view shows insular cortex forming the inner wall of lateral fissure. Claustrum is on the medial side of the cortex.

Back to Figure

Default mode network is internally directed, and posterior parietal cortex, and ventromedial prefrontal cortex are highlighted.

In salience network, anterior cingulate cortex, and anterior insular cortex are highlighted.

Central executive network is externally directed, and dorsolateral prefrontal cortex and posterior cingulate cortex are highlighted.

Dynamic switching occurs between the networks.

Back to Figure

When presented with masked words, activity is detected in the right occipital lobe after 172 milliseconds. There is no spread of activity through other lobes after 244 and 476 milliseconds.

When presented with visible words, activity is detected in the occipital lobe after 156 milliseconds. Brain activity is spread to the frontal lobe by 244 milliseconds and back

to the occipital lobe by 476 milliseconds.
Back to image

The levels of consciousness in the decreasing order of activity are as follows:

- Conscious controls (n equals 110)
- Locked-in syndrome (n equals 5)
- Minimally conscious state (n equals 7)
- Vegetative state (n equals 33)

Back to Figure

The illustrations show 31 numbered electrodes of E E G placed on a patient's scalp. From front to back, electrodes 13, 7, 31, 17, 24, 23, 11, 8, 29, 28, 9, and 15 are on the left hemisphere, electrodes 1, 22, 2, 27, and 3 are on the middle, and electrodes 12, 4, 30, 16, 21, 20, 5, 10, 26, 25, 18, 6, and 14 are on the right hemisphere.

1. Shock left midfinger: Primary somatosensory cortex and secondary somatosensory cortex in the right hemisphere, and visual cortex are highlighted. Synchrony was observed between the following electrode pairs: 3 and 22, 3 and 2, 3 and 21, 3 and 5, 3 and 26, and 15 and 26.
2. Shock right midfinger: Primary somatosensory cortex and secondary somatosensory cortex in the left hemisphere, and visual cortex are highlighted. Synchrony was observed between the following electrode pairs:3 and 22, 3 and 2, 3 and 23, 3 and 8, 3 and 28, and 15 and 23.

Back to Figure

A man stands near a corner of a room. Another man stands in front of him, holding a mirror directly in front of his right eye. The second man's left eye and the first man's right eye are aligned. The second man raises his arm to the wall, such that the reflection of the hand on the mirror is observed by his right eye.

Back to Figure

The photos show a plate of cookies, a glass jar, teapot, milk pot, glass jar, and a cup. In the first photo, a hand reaches for the cup filled with beverage and holds it. In the second photo, the jar is opened, one of the pots are tipped over, the crumbs are around the cookie plate in which the cookies are half eaten, and a tissue is beside the tea pot. A hand holds the cup by its handle.

Back to Figure

The patient looks at an image of a house with smoke coming out from the chimney and a snowman on the left side and a bird's talon on the right side. In the patient's brain, the image of the bird's talon is on the left side of the brain and the image of the house, and the snowman is on the right side. Eight cards are in front of the patient with the following images from left to right: Shovel, crate, hammer, rake, a hand, microscope, bird, and bell. The patient points to the shovel with the left hand and to the bird with the right hand.

Back to Figure

When listening to a traumatic memory script during traumatic identity state, the areas of greater blood flow are the amygdala, ventral surface of the temporal lobe, and the base of the parietal lobe.

When listening to a traumatic memory script during neutral identity state, the areas of greater blood flow are the prefrontal lobe and few regions on the dorsal surface of the

brain.
Back to Figure

The vertical axis is labeled volume in millimeters cubed, and ranges from 1000 to 2400 in increments of 200. The approximate data from the graph are tabulated below.

GLOSSARY

aberrant salience hypothesis
The hypothesis that heightened levels of dopamine increase attentional and motivational circuits to make ordinary environmental features seem significant.

ablation
Removal of brain tissue.

absolute refractory period
A brief period following the peak of the action potential when the sodium ion channels are inactivated and the neuron cannot be fired again.

absorptive phase
The period of a few hours following a meal during which the body relies on the nutrients arriving from the digestive system.

ACC
See *anterior cingulate cortex*.

accommodation
Changing of the lens shape to focus light onto the retina; the ciliary muscles contract to make the lens rounder for a near object and relax to flatten the lens for a far object.

action potential
An all-or-none electrical signal of a neuronal membrane that contains an abrupt voltage depolarization and return to resting potential; allows the neuron to communicate over long distances.

activating effects
Hormonal effects on sexual development that can occur at any time in an individual's life; their duration depends on the presence of the hormone.

acute

A term referring to symptoms that develop suddenly and are usually more responsive to treatment.

addiction
A preoccupation with obtaining a drug, compulsive use of the drug in spite of adverse consequences, and a high tendency to relapse after quitting. Addiction is distinct from dependence.

adequate stimulus
The energy form for which a receptor is specialized.

ADHD
See *attention-deficit/hyperactivity disorder*.

adoption study
A technique for studying the roles of heredity and environment by comparing the similarity of adopted children to their biological parents with their similarity to their adoptive parents.

affective aggression
Hostile or violent behavior that is characterized by impulsiveness and emotional arousal.

agency
The sense that an action or effect is due to oneself rather than to another person or an external force.

aggression
Forceful or assertive behavior that is intended to harm or control another individual.

agonist
Any substance that mimics or enhances the effect of a neurotransmitter.

agonist treatment
Addiction treatment that replaces the addicting drug with another drug that has a similar effect.

agraphia
The inability to write due to brain damage.

alcohol

Ethanol, a drug fermented from fruits, grains, and other plant products, which acts at many brain sites to produce euphoria, anxiety reduction, motor incoordination, and cognitive impairment.

alexia
The inability to read due to brain damage.

allele
An alternate version of a gene; can be dominant or recessive.

all-or-none law
The principle that an action potential occurs at full strength or it does not occur at all.

Alzheimer's disease
A disorder characterized by progressive brain deterioration and impairment of memory and other mental abilities; the most common cause of dementia.

amino acids
The building blocks of peptides, which in turn make up proteins. In digestion, the result of the breakdown of proteins.

amphetamine
One of a group of synthetic drugs that produce euphoria and increase confidence and concentration.

amygdala
A limbic system structure located near the lateral ventricle in each temporal lobe that is involved with a variety of emotions, especially fear and anxiety, and with sexual behavior, aggression, and learning, especially in emotional situations.

analgesic
Pain relieving.

androgen insensitivity syndrome
A form of 46,XY intersex involving insensitivity to androgen because of a genetic absence of androgen receptors. The person has male sex chromosomes and internal sex organs, but external sex characteristics are feminized or ambiguous.

androgens
A class of hormones responsible for a number of male characteristics and functions.

angiotensin II
A hormone that signals lowered blood volume and, thus, volemic thirst to the brain.

angular gyrus
A gyrus at the border of the parietal and occipital lobes containing pathways that connect the visual area with auditory, visual, and somatosensory association areas in the temporal and parietal lobes. Damage results in alexia and agraphia.

anorexia nervosa
An eating disorder in which the person restricts food intake to maintain weight at a level so low that it is threatening to health.

ANS
See *autonomic nervous system*.

antagonist
Any substance that reduces the effect of a neurotransmitter.

antagonistic muscles
Contractile tissues that produce opposite movements at a joint.

antagonist treatment
A form of treatment for drug addiction using drugs that block the effects of the addicting drug.

anterior
Toward the front.

anterior cingulate cortex (ACC)
A part of the limbic system important in attention, decision making, impulse control, emotion, and possibly consciousness.

anterograde amnesia
An impairment in forming new memories.

antidrug vaccine

A form of anti-addiction treatment using molecules that attach to the drug and stimulate the immune system to make antibodies that will break down the drug.

antisense RNA
A technology that temporarily disables a targeted gene or reduces its effectiveness.

anxiolytic
Anxiety reducing.

aphasia
Language impairment caused by damage to the brain.

apotemnophilia
See *body integrity identity disorder*.

arcuate nucleus (ARC)
A structure in the hypothalamus that monitors the body's nutrient condition and regulates eating behavior; it is considered the master hypothalamic center for food intake control.

area postrema
A brain area unprotected by the blood-brain barrier; blood-borne toxins entering here induce vomiting.

arousal theory
The hypothesis that people behave in ways that keep them at their preferred level of arousal.

ASD
See *autism spectrum disorder*.

association area
Cortical areas that carry out further processing beyond what the primary projection area does, often combining information from other senses.

associative long-term potentiation
Strengthening of a weak synapse when it and a strong synapse on the same postsynaptic neuron are active simultaneously.

attention

The brain's means of allocating its limited resources by focusing on some neural inputs to the exclusion of others.

attention-deficit/hyperactivity disorder (ADHD)
A disorder that develops during childhood and is characterized by impulsiveness, inability to sustain attention, learning difficulty, and hyperactivity.

auditory cortex
The area of cortex on the superior temporal gyrus, which is the primary projection area for auditory information.

auditory object
A sound that we recognize as having an identity that is distinct from other sounds.

autism spectrum disorder (ASD)
A set of neurodevelopmental disorders characterized by social deficits, communication difficulties, and repetitive behaviors.

autistic savant
An individual with autism with an isolated exceptional capability.

autoimmune disorder
A disorder in which the immune system attacks the body's own cells.

autonomic nervous system (ANS)
One of the two branches of the peripheral nervous system; it is composed of the sympathetic and parasympathetic nervous systems, which control smooth muscle, glands, and the heart and other organs.

autoradiography
A technique for identifying brain structures involved in an activity; it involves injecting a radioactive substance (such as 2-DG) that will be absorbed most by the more active neurons, which then will show up on an X-ray image.

autoreceptor
A receptor on a neuron terminal that senses the amount of transmitter in the synaptic cleft and reduces the presynaptic neuron's output when the level is excessive.

aversive treatment
A form of addiction treatment that causes a negative reaction when the person takes the drug.

axon
An extension from a neuron's cell body that carries information to other locations.

axon terminal
A swelling on the branches at the end of a neuron that contains neurotransmitters; also called an *end bulb*.

barbiturate
A class of drugs that act selectively on higher cortical centers, especially those involved in inhibiting behavior, so they produce talkativeness and increased social interaction. In higher doses, they act as sedatives and hypnotics. They are used to treat anxiety, aid sleep, and prevent epileptic convulsions.

basal ganglia
The caudate nucleus, putamen, and globus pallidus, located subcortically in the frontal lobes; they participate in motor activity by integrating and smoothing movements using information from the primary and secondary motor areas and the somatosensory cortex.

basal metabolism
The amount of energy required to fuel the brain and other organs and to maintain body temperature.

basilar membrane
The membrane in the cochlea that separates the cochlear canal from the tympanic canal and on which the organ of Corti is located.

bath salts
Any one of several synthetic derivatives of the *Catha edulis* plant that have amphetamine-like effects.

B cell
A type of immune cell that fights intruders by producing antibodies that attack a particular intruder.

behavioral neuroscience
The branch of psychology that studies the relationships between behavior and the body, particularly the brain.

benzodiazepine
A class of drugs that produce anxiety reduction, sedation, and muscle relaxation by stimulating benzodiazepine receptors on the $GABA_A$ complex, facilitating GABA binding.

binding problem
The question of how the brain combines all the information about an object into a unitary whole.

binge eating disorder
A disorder characterized by frequent consumption of excessive amounts of food during a short interval of time and a feeling of loss of control over what and how much is eaten.

bipolar disorder
Depression and mania that occur together in alternation.

blindsight
The ability of cortically blind individuals to respond to visual stimuli that are outside conscious awareness.

blood-brain barrier
The brain's protection from toxic substances and neurotransmitters in the bloodstream; the small openings in the capillary walls prevent large molecules from passing through unless they are fat soluble or carried through by special transporters.

BMI
See *body mass index*.

body integrity identity disorder
The desire, in individuals with no apparent brain damage or mental illness, to have a healthy limb amputated.

body mass index (BMI)
The person's weight in kilograms divided by the squared height in meters; an indication of the person's deviation from the ideal

weight for the person's height.

brain interpreter
A hypothetical mechanism that integrates all the cognitive processes going on simultaneously in other modules of the brain.

Broca's aphasia
Language impairment caused by damage to Broca's area and surrounding cortical and subcortical areas.

Broca's area
The area anterior to the precentral gyrus (motor cortex) that sends output to the facial motor area to produce speech and also provides grammatical structure to language.

BSTc
See *central subdivision of the bed nucleus of the stria terminalis*.

bulimia nervosa
An eating disorder involving bingeing on food, followed by purging by vomiting or using laxatives.

caffeine
A drug that produces arousal, increased alertness, and decreased sleepiness; the active ingredient in coffee and tea.

CAH
See *congenital adrenal hyperplasia*.

cannabinoids
A group of compounds that includes the active ingredient in marijuana (tetrahydrocannabinol, or THC) and the endogenous cannabinoid receptor ligands, anandamide, and 2-arachidonyl glycerol (2-Ara-Gl). Cannabinoids act as retrograde messengers.

cardiac muscles
The strong contractile tissues that make up the heart.

castration
Removal of the gonads (testes or ovaries).

cataplexy
A disorder in which a person has a sudden loss of muscle strength (atonia) like that seen in REM sleep; the person may fall to the floor but remains awake.

CCK
See *cholecystokinin*.

cell body
The largest part of a neuron, which contains the cell's nucleus, cytoplasm, and structures that produce proteins, convert nutrients into energy, and eliminate waste materials; also called the *soma*.

central executive network
A brain network that controls attention and working memory; unlike the default mode network, it is task oriented.

central nervous system (CNS)
The part of the nervous system made up of the brain and spinal cord.

central pattern generator (CPG)
A neuronal network that produces a rhythmic pattern of motor activity, such as that involved in walking, swimming, flying, or breathing.

central subdivision of the bed nucleus of the stria terminalis (BSTc)
A structure that is larger in males than in females and in MtF transsexual individuals; it is closely connected to the amygdala, hippocampus, and prefrontal cortex, and in rats it mediates pheromone signaling.

central sulcus
The groove between the precentral gyrus and the postcentral gyrus that separates the frontal lobe from the parietal lobe in each hemisphere.

cerebellum
A structure in the hindbrain that contributes the order of muscular contractions and their precise timing to intended movements and helps maintain posture and balance. It is also

necessary for learning motor skills and contributes to nonmotor learning and cognitive activities.

cerebral hemispheres
The large, wrinkled structures that are the dorsal or superior part of the brain and that are covered by the cortex.

cerebrospinal fluid
Liquid in the ventricles and spinal canal that carries material from the blood vessels to the central nervous system and transports waste materials in the other direction. It also helps cushion the brain and spinal cord.

cholecystokinin (CCK)
A peptide hormone released as food passes into the duodenum; CCK acts as a signal to the brain that reduces meal size.

chronic
A term referring to symptoms that develop gradually and persist for a long time with poor response to treatment.

chronic pain
Pain that persists after healing has occurred, or beyond the time in which healing would be expected to occur.

circadian rhythm
A rhythm that is a day in length, such as the wake-sleep cycle.

circannual rhythm
A rhythm that is a year in length, such as migration and seasonal mood.

circuit formation
The third stage of nervous system development, in which the developing neurons send processes to their target cells and form functional connections.

circuit pruning
The fourth stage of nervous system development, in which neurons that are unsuccessful in finding a place on the appropriate target cell, or that arrive late, die and excess synapses are eliminated.

CNS
See *central nervous system*.

cocaine
A drug extracted from the South American coca plant that produces euphoria, decreased appetite, increased alertness, and relief from fatigue.

cochlea
The snail-shaped structure where the ear's sound-analyzing structures are located.

cochlear canal
The middle canal in the cochlea, which contains the organ of Corti.

cocktail party effect
The ability to sort out meaningful auditory messages from a complex background of sounds.

cognitive theory
A theory that states that a person relies on a cognitive assessment of the stimulus situation to identify which emotion is being experienced; physiological arousal determines the intensity of the emotional experience.

coincidence detectors
Neurons that fire most when they receive input from both ears at the same time; they are involved in sound localization.

color agnosia
Loss of the ability to perceive colors due to brain damage.

color blindness
A condition when one or more color-sensitive cones is functionally impaired or absent, leading to difficulty distinguishing certain colors. Also called *color vision deficiency*.

color constancy
The ability to recognize the natural color of an object regardless of the brightness or wavelength of illuminating light.

compensation

A response to nervous system injury, in which surviving presynaptic neurons sprout new terminals, postsynaptic neurons add more receptors, or surrounding tissue takes over functions.

complementary colors
Colors that cancel each other out to produce a neutral gray or white.

complex cell
A type of cell in the visual cortex that continues to respond (unlike simple cells) when a line or an edge moves to a different location.

complex sound
A sound composed of more than one pure tone.

computed tomography (CT)
An imaging technique that produces a series of X-rays taken from different angles; these are combined by a computer into a three-dimensional image of the brain or another part of the body.

concordance rate
The proportion of cases in which a pair of related individuals shares a characteristic.

congenital adrenal hyperplasia (CAH)
A form of 46,XX intersex characterized by XX chromosomes, female internal sex organs, and ambiguous or masculinized external sex characteristics. It is caused by excess production of androgens during prenatal development.

congenital insensitivity to pain
A condition, present at birth, in which the person is insensitive to pain due to a genetic pathology in the peripheral nervous system.

consolidation
The process in which the brain forms a permanent representation of a memory.

Coolidge effect
An increase in sexual activity when the variety of sexual partners increases; named after former president Calvin

Coolidge.

corpus callosum
The largest of the groups of neurons connecting the two cerebral hemispheres.

correlation
The degree to which two variables are related, such as the IQs of siblings; it is measured by the correlation coefficient, a statistic that varies between the values of 0.0 and ±1.0.

correlational study
A study in which the researcher does not control an independent variable but determines whether two variables are related to each other.

cortex
The grayish 1.5- to 4-mm-thick surface of the hemispheres, composed mostly of cell bodies, where the highest-level processing occurs in the brain.

cortisol
A hormone released by the adrenal cortex that produces physiological stress responses, including increases in metabolism, glucose availability, and blood supply to the skeletal muscles. The increase is more sustained than that produced by epinephrine and norepinephrine.

cranial nerves
The 12 pairs of axonal bundles that enter and leave the underside of the brain; part of the peripheral nervous system.

CT
See *computed tomography*.

Dale's principle
The theory that a neuron is able to release only one neurotransmitter.

db
See *diabetes gene*.

DBS

See *deep brain stimulation*.

deception
In research, failing to tell the participants the exact purpose of the research or what will happen during the study or actively misinforming them.

declarative memory
The memory process that records memories of facts, people, and events that the person can verbalize, or *declare*.

deep brain stimulation (DBS)
Electrical stimulation of the brain through implanted electrodes.

default mode network
Portions of the frontal, parietal, and temporal lobes that are active when the brain is at rest or focused internally; its activity is thought to represent preparedness for action.

delirium tremens
A reaction in some cases of withdrawal from alcohol, including hallucinations, delusions, confusion, and, in extreme cases, seizures and possible death.

dementia
Substantial loss of memory and other cognitive abilities usually, but not necessarily, in the elderly.

dendrites
Extensions that branch out from the neuron cell body and receive information from other neurons.

dendritic spines
Outgrowths from the dendrites that partially bridge the synaptic cleft and make the synapse more sensitive.

deoxyribonucleic acid (DNA)
A double-stranded chain of chemical molecules that looks like a ladder that has been twisted around itself; genes are composed of DNA.

dependence

The need to continue taking a drug to avoid the physical and psychological symptoms of withdrawal. Dependence is distinct from addiction.

depressant
A drug that reduces central nervous system activity.

depression
An intense feeling of sadness.

dermatome
A segment of the body served by a spinal nerve.

diabetes
An insulin disorder in which the person produces too little insulin (type 1), resulting in overeating with little weight gain, or the person's brain is insensitive to insulin (type 2), resulting in overeating with weight gain.

diabetes gene
A gene on chromosome 4 that produces diabetes and obesity; mice with the gene are insensitive to leptin.

DID
See *dissociative identity disorder*.

diffusion tensor imaging (DTI)
A variant of MRI that measures movement of water molecules to image brain pathways and quantify their quality.

dihydrotestosterone
A derivative of testosterone that masculinizes the genitals of males.

dissociative identity disorder (DID)
The disorder previously known as multiple personality, which involves shifts in consciousness and behavior that appear to be distinct personalities or selves.

distributed
A term referring to any brain function that occurs across a relatively wide area of the brain.

DNA
See *deoxyribonucleic acid*.

dominant
A term referring to an allele that will produce its effect regardless of which allele it is paired with in the fertilized egg.

dopamine hypothesis
The hypothesis that schizophrenia involves excess dopamine activity in the brain.

dorsal
Toward the back side of the body.

dorsal root
The branch of a spinal nerve through which neurons enter the spinal cord.

dorsal stream
The visual processing pathway that extends into the parietal lobes; it is especially concerned with the location of objects in space.

Down syndrome
Intellectual disability characterized by IQs in the 40 to 55 range, usually caused by the presence of an extra 21st chromosome.

drive
An aroused condition resulting from a departure from homeostasis, which impels the individual to take appropriate action, such as eating.

drive theory
A hypothesis based on the assumption that an unmet need will result in behavior that will satisfy that need in order to maintain a condition of homeostasis.

drug
Any medicine or other substance that, on entering the body, changes the body's functioning.

dualism
The idea that the mind and the brain are separate.

duodenum
The first section of the small intestine, where most digestion occurs.

dyslexia
An impairment of reading, which can be developmental or acquired through brain damage.

ECT
See *electroconvulsive therapy*.

EEG
See *electroencephalogram*.

electroconvulsive therapy (ECT)
The application of 70 to 130 volts of electricity to the head of a lightly anesthetized patient, which produces a seizure and convulsions; a treatment for major depression.

electroencephalogram (EEG)
A measure of brain activity recorded from two electrodes on the scalp over the area of interest and connected to an electronic amplifier; this detects the combined electrical activity of all the neurons between the two electrodes.

electromagnetic spectrum
A variety of energy forms, ranging from high-frequency gamma rays at one extreme to very-low-frequency electrical currents on the other.

electron microscope
See *transmission electron microscope* and *scanning electron microscope*.

electrostatic pressure
The force by which like-charged ions are repelled by each other and opposite-charged ions are attracted to each other.

embryo
An organism in the early prenatal period; in humans, during the first eight weeks.

emotion

A state of feelings accompanied by an increase or a decrease in physiological activity and often by characteristic facial expression and behavior.

empiricism
The procedure of obtaining information through observation.

endogenous
Generated within the body; usually used to refer to natural ligands for neurotransmitter receptors.

endorphins
Substances produced in the body that function both as neurotransmitters and as hormones and that act on opioid receptors in many parts of the nervous system.

epigenetic
A term referring to modifications to DNA that turn genes “on” or “off,” without changing the gene’s DNA sequence.

EPSP
See *excitatory postsynaptic potential*.

equipotentiality
The idea that the brain functions as a whole; the opposite of localization.

estrogens
A class of hormones responsible for a number of female characteristics and functions; produced by the ovaries in women and, to a lesser extent, by the adrenal glands in males and females.

estrus
A period when a nonhuman female animal is ovulating and sex hormone levels are high.

euphoric
A term referring to a drug’s ability to produce a sense of happiness or ecstasy; many abused drugs produce euphoria.

Eustachian tube

The connection between the middle ear and the oral cavity, the function of which is to equalize air pressure differences between the outside of the head and the middle ear.

event-related potential
An EEG technique for measuring the brain's responses to brief stimulation; it involves presenting a stimulus repeatedly and averaging the EEG over all the presentations to cancel out random activity, leaving the electrical activity associated with the stimulus.

excitatory postsynaptic potential (EPSP)
A partial depolarization of the dendrites and cell body, which makes the neuron more likely to fire.

experimental study
A study in which the researcher manipulates an independent variable and observes its effect on one or more dependent variables.

fabrication
In research, deliberately falsifying, altering, or manipulating data or results.

familial
A term referring to a characteristic that occurs more frequently among relatives of a person with the characteristic than it does in the population.

family study
A technique for studying the roles of heredity and environment by assessing how strongly a characteristic is shared among relatives.

fasting phase
The period following the absorptive phase, when the glucose level in the blood drops and the body must rely on its energy stores.

fatty acids
A breakdown product of fat, which supplies the muscles and organs of the body (except for the brain).

fetal alcohol syndrome
A condition caused by the mother's use of alcohol during the third trimester of pregnancy; neurons fail to migrate properly, often resulting in intellectual disability; the leading cause of intellectual disability in the Western world.

fetus
An organism after the initial prenatal period; in humans, after the first eight weeks.

FFA
See *fusiform face area*.

fissure
A deep groove between gyri of the cerebral hemispheres that is larger than a *sulcus*.

fMRI
See *functional magnetic resonance imaging*.

force of diffusion
The pressure exerted by ions from an area of greater concentration to an area where they are less concentrated.

form vision
The detection of an object's boundaries and features, such as texture.

46,XX intersex
Possession of ambiguous or male external genitalia in a person with two X chromosomes in each cell, due to excess androgens or hormone treatment during gestation.

46,XY intersex
Possession of ambiguous or female external genitalia in a person with an X and a Y chromosome in each cell, due to incomplete masculinization.

fovea
A 1.5-mm-wide area in the middle of the retina in which cones are most concentrated and visual acuity and color discrimination are greatest.

fragile X syndrome
A form of intellectual disability caused by excessive CGG repeats in the *FMR1* gene; IQ is typically below 75.

frequency
A characteristic of sound; the number of cycles or waves of alternating compression and decompression of the vibrating medium that occur in a second. For the psychological perception of frequency, see *pitch*.

frequency-place theory
The hypothesis that frequency following individual neurons accounts for the discrimination of frequencies up to about 200 Hz, and higher frequencies are represented by the place of greatest activity on the basilar membrane.

frequency theory
Any one of several hypotheses of auditory frequency analysis that state that the frequency of a sound is represented in the firing rate of each neuron or a group of neurons.

frontal lobe
The area of each cerebral hemisphere anterior to the central sulcus and superior to the lateral fissure.

functional magnetic resonance imaging (fMRI)
A brain-imaging procedure that measures brain activation by detecting increases in blood flow and oxygen usage in active neural structures.

fusiform face area (FFA)
A part of the inferior temporal lobe important in face identification. See also *prosopagnosia*.

ganglion
A group of cell bodies in the peripheral nervous system.

gate control theory
The hypothesis that pressure signals arriving in the brain trigger an inhibitory message that travels back down the spinal cord, where it closes a neural “gate” in the pain pathway.

gender

The behavioral characteristics associated with being male or female.

gender dysphoria
The distress that people may feel when their gender identity does not match their sex at birth.

gender identity
A person's subjective feeling of being male, female, a combination, or genderless.

gender role
A set of behaviors society considers appropriate for people of a given biological sex.

gene
The biological unit that directs cellular processes and transmits inherited characteristics.

gene expression
The translation of a gene's encoded information into the production of proteins, determining the gene's functioning.

genetic engineering
Manipulation of an organism's genes or their functioning.

gene therapy
Treatment of a disorder by gene manipulation.

gene transfer
Insertion of a gene from another organism into a recipient's cells, usually within a virus.

genome
The entire collection of genes in the chromosomes of a species.

genotype
The combination of genes an individual has.

ghrelin
An orexigenic neuropeptide hormone that is synthesized in the stomach and released into the bloodstream during fasting.

glial cell
A nonneural cell that provides several supporting functions to neurons, including myelination.

glucagon
A hormone released by the pancreas that stimulates the liver to transform stored glycogen back into glucose during the fasting phase.

glucose
One of the sugars; the body's main source of energy, reserved for the nervous system during the fasting phase; a major signal for hunger and satiation.

glutamate theory
The hypothesis that NMDA receptor hypofunction results in glutamate and dopamine increases that produce positive and negative symptoms of schizophrenia.

glycerol
A breakdown product of fats, which is converted to glucose for the brain during the fasting period.

glycogen
The form in which glucose is stored in the liver and muscles during the absorptive phase; it is converted back to glucose for the brain during the fasting phase.

Golgi stain
A staining method that randomly stains about 5% of neurons, which makes them stand out individually.

Golgi tendon organs
Receptors that detect tension in a muscle.

gonads
The primary reproductive organs: testes in the male or ovaries in the female. An individual can have only one of the two types of gonads.

graded potential
A voltage change in a neuron that varies with the strength of the stimulus that initiated it.

grammar
The consistent set of rules of a particular language.

growth cone
A formation at the tip of a migrating neuron that samples the environment for directional cues.

gyrus
A ridge in the cerebral cortex; the area between two sulci.

head-related transfer function (HRTF)
Spectral frequency alterations to a sound as it passes through the pinna and auditory canal, as well as through the head and other parts of the body. One of the cues for localizing the direction of a sound source.

Hebb rule
The principle stating that if an axon of a presynaptic neuron is active while the postsynaptic neuron is firing, the synapse between them will be strengthened.

heritability
The percentage of the variation among individuals in a characteristic that can be attributed to heredity.

heroin
A major drug of addiction synthesized from morphine.

heterozygous
Having a pair of alleles for a specific characteristic that are different from each other.

hierarchical processing
A type of processing in which lower levels of the nervous system analyze their information and pass the results on to the next higher level for further analysis.

homeostasis
A body system seeks and maintains this condition of balance or equilibrium and has mechanisms to minimize changes to the system.

homozygous

Having a pair of alleles for a specific characteristic that are identical to each other.

HRTF
See *head-related transfer function*.

Human Connectome Project
A large-scale cooperative effort to map the circuits in the human brain.

Human Genome Project
An international project with the goal of mapping the location of all the genes on the human chromosomes and determining the base sequences of the genes.

Huntington's disease
A degenerative disorder of the motor system involving cell loss in the striatum and cortex.

hydrocephalus
A disorder in which cerebrospinal fluid fails to circulate and builds up in the cerebral ventricles, crowding out neural tissue and usually causing intellectual disability.

hyperpolarization
A negative change in a neural membrane's voltage, which is inhibitory and makes an action potential less likely to occur. See *inhibitory postsynaptic potential* for the synaptic effect.

hypnotic
Sleep inducing.

hypocretin
See *orexin*.

hypofrontality
Reduced activity in several frontal regions that control working memory, attention, behavioral inhibition, and the individual's response to the environment.

hypogonadism
A disorder in which the gonads (testes or ovaries) fail to make normal levels of sexual hormones.

hypothalamus
A subcortical structure in the forebrain just below the thalamus that plays a major role in controlling emotion and motivated behaviors, such as eating, drinking, and sexual activity.

hypothalamus-pituitary-adrenal axis
A group of structures that help the body cope with stress.

hypovolemic thirst
A fluid deficit that occurs when the blood volume drops due to a loss of extracellular water.

ID
See *intellectual disability*.

immune system
The cells and cell products that kill infected and malignant cells and protect the body against foreign substances, including bacteria, viruses, toxins, and pollen.

immunocytochemistry
A procedure for labeling cellular components such as receptors, neurotransmitters, or enzymes by using a dye attached to an antibody designed to attach the component.

impulsive aggression
See *reactive aggression*.

INAH3
See *third interstitial nucleus of the anterior hypothalamus*.

incentive theory
A theory that recognizes that people are motivated by external stimuli (incentives), not just internal needs.

incidence
The number of individuals who develop a condition across a specific amount of time (such as a year).

inferior
Below another structure.

inferior colliculi

The part of the tectum in the brain stem that is involved in auditory functions, such as locating the direction of sounds.

inferior temporal cortex
An area in the lower part of the temporal lobe that plays a major role in the visual identification of objects.

inflammatory soup
A combination of histamine, proteins (bradykinin and substance P), lipids (prostaglandins), neurotransmitters (serotonin), and cytokines that causes inflammation.

informed consent
Voluntary agreement to participate in a study after receiving full information about any risks, discomfort, or other adverse effects that might occur.

inhibitory postsynaptic potential (IPSP)
A hyperpolarization of the dendrites and cell body, which makes a neuron less likely to fire.

inner hair cells
A single row of about 3,500 hair cells located on the basilar membrane toward the inside of the cochlea's coil; they produce most, if not all, of the auditory signal.

in situ hybridization
A procedure for locating gene activity; involves constructing strands of complementary DNA that will dock with strands of messenger RNA. The complementary DNA is radioactive, so autoradiography can be used to locate the gene activity.

insomnia
The inability to sleep or to obtain quality sleep, to the extent that the person feels inadequately rested.

instinct
A complex behavior that is automatic and unlearned and occurs in all the members of a species.

instrumental aggression
See *proactive aggression*.

insulin
A hormone secreted by the pancreas that enables entry of glucose into cells (not including the nervous system) during the absorptive phase and facilitates storage of excess nutrients.

intellectual disability (ID)
Limitation in intellectual functioning (reasoning, learning, problem solving) and adaptive behavior that is developmental in origin.

intelligence
The capacity for learning, reasoning, and understanding.

intelligence quotient (IQ)
The measure typically used for intelligence.

intensity
In audition, the physical energy in a sound; the sound's amplitude. For the psychological perception of intensity, see *loudness*.

interaural level difference
A binaural cue to the location of a sound coming from one side that results from the sound shadow created by the head; most effective above 2000 to 3000 Hz.

interaural timing difference (ITD)
A binaural cue to the location of a sound coming from one side due to the time the sound requires to travel the distance between the ears; most effective for low-frequency sounds.

interneuron
A neuron that has a short axon or no axon at all and connects one neuron to another in the same part of the central nervous system.

iodopsin
A group of three photopigments found in cones; one form is sensitive to red light, one is sensitive to green light, and one is sensitive to bluish-violet light.

ion

An element or atom that is charged because it has lost or gained one or more electrons.

ionotropic receptor
A receptor that is part of the ion channel and opens the channel immediately to produce quick reactions required for muscle activity and sensory processing.

IPSP
See *inhibitory postsynaptic potential*.

IQ
See *intelligence quotient*.

James-Lange theory
The idea that physiological arousal precedes and is the cause of an emotional experience and that the pattern of arousal identifies the emotion.

knockdown technique
A genetic engineering technique in which a gene's activity is reduced by interfering with its expression.

knockout technique
A genetic engineering technique in which a nonfunctioning gene mutation is inserted during the embryonic stage.

language
A structured system of communication with a common set of grammatical, lexical, and organizational rules.

language acquisition device
A part of the brain hypothesized to be dedicated to learning and controlling language.

lateral
Toward the side.

lateral fissure
The fissure that separates the temporal lobe from the frontal and parietal lobes.

lateral hypothalamus (LH)

A nucleus of the hypothalamus that initiates eating and controls several aspects of feeding behavior and metabolic responses; it is also involved in aggression and waking arousal.

lateral inhibition
A method of enhancing neural information in which each neuron's activity inhibits the activity of its neighbors and in turn its activity is inhibited by them.

L-dopa
See *levodopa*.

learned taste aversion
Learned avoidance of a food (based on its taste) eaten prior to becoming ill.

learned taste preference
Preference for a food containing a needed nutrient (identified by the food's taste), learned, presumably, because the nutrient makes the individual feel better.

leptin
A hormone secreted by fat cells, which is proportional to the percentage of body fat and which signals fat level to the brain.

lesioning
Surgical damage to neural tissue, typically using electrical current, heat, a chemical, or a microscalpel. Lesions occur naturally as a result of trauma, disease, or developmental error.

leukocytes
White blood cells, which include macrophages, T cells, and B cells; part of the immune system.

levodopa (L-dopa)
The precursor for dopamine; it is used to treat Parkinson's disease.

Lewy bodies
Abnormal clumps of protein that form within neurons, found in some patients with Parkinson's disease and Alzheimer's disease.

limbic system
A group of forebrain structures arranged around the upper brain stem that have roles in emotion, motivated behavior, and learning.

lithium
A metal administered in the form of lithium carbonate; the medication of choice for treating bipolar disorder.

localization
The idea that specific parts of the brain carry out specific functions.

longitudinal fissure
The large fissure that extends the length of the brain, separating the two cerebral hemispheres.

long-term depression (LTD)
Weakening of a synapse when stimulation of presynaptic neurons is insufficient to activate the postsynaptic neurons.

long-term potentiation (LTP)
An increase in synaptic strength that occurs when presynaptic neurons and postsynaptic neurons are active simultaneously.

loudness
The term for our *experience* of sound intensity.

LTD
See *long-term depression*.

LTP
See *long-term potentiation*.

macrophage
A type of leukocyte that ingests intruders.

magnetic resonance imaging (MRI)
An imaging technique that involves measuring the radio-frequency waves emitted by hydrogen atoms when they are subjected to a strong magnetic field. Because different structures have different concentrations of hydrogen atoms, the waves can be used to form a detailed image of the brain.

magnocellular system
A division of the visual system, extending from the retina through the visual association areas, that is specialized for brightness contrast and for movement.

major depressive disorder (MDD)
A disorder involving feelings of sadness to the point of hopelessness for weeks at a time, along with slowness of thought, sleep disturbance, and loss of energy and appetite and the ability to enjoy life; in some cases, the person is also agitated or restless. Sometimes called *unipolar depression*.

mania
A disorder involving excess energy and confidence that often leads to grandiose schemes, decreased need for sleep, increased sexual drive, and, often, abuse of drugs.

marijuana
The dried and crushed leaves and flowers of the plant *Cannabis sativa*.

materialistic monism
The view that the body and the mind and everything else are physical.

MDD
See *major depressive disorder*.

medial
Toward the middle.

medial amygdala
The part of the amygdala that apparently responds to sexually exciting stimuli. In both male and female rats, it is active during copulation, and it causes the release of dopamine in the MPOA.

medial preoptic area (MPOA)
A part of the preoptic area of the hypothalamus that appears to be important for sexual performance, but not sexual motivation, in male and female rats.

median preoptic nucleus (MnPO)

A nucleus of the hypothalamus that initiates drinking in response to osmotic and volumetric deficits.

medulla
The lower part of the hindbrain; its nuclei are involved with control of essential life processes, such as cardiovascular activity and respiration.

melatonin
A hormone secreted by the pineal gland that induces sleepiness; in the normal circadian rhythm, it is released about 2hours before bedtime.

meninges
A three-layered membrane that encloses and protects the brain.

mesocorticolimbic dopamine system
The ventral tegmental area and the brain regions receiving its dopaminergic projections, including the nucleus accumbens, prefrontal cortex, amygdala, and hippocampus. The system is important in reward and addiction.

mesolimbic pathway
A dopaminergic pathway originating in the ventral tegmental area and projecting to several locations in the limbic system, particularly the nucleus accumbens. The pathway is important in responding to rewarding stimuli.

messenger ribonucleic acid (mRNA)
A copy of one strand of DNA that moves out of the nucleus to direct protein construction.

metabotropic receptor
A receptor on a neuron membrane that opens ion channels slowly via a second messenger and produces long-lasting effects.

methadone
A synthetic opioid used as an agonist treatment for opiate addiction.

methylation

Attachment of a methyl group to DNA, which suppresses a gene's activity. See also *epigenetic*.

microglia
Glial cells that provide immune protection in the central nervous system by acting as macrophages.

midbrain
The middle part of the brain, consisting of the tectum (roof) on the dorsal side and the tegmentum on the ventral side.

migration
In brain development, movement of newly formed neurons from the ventricular zone to their final destinations.

mind-brain problem
The issue of what the mind is and what its relationship is to the brain.

mirror neurons
Cortical neurons that respond when engaging in an act and while observing the same act in others; found in the premotor cortex, supplementary motor area, primary somatosensory cortex, and inferior parietal cortex.

MnPO
See *median preoptic nucleus*.

model
A proposed mechanism for how something works.

modular processing
The segregation of the various components of processing in the brain into separate locations.

monism
The idea that the mind and the body consist of the same substance.

monoamine hypothesis
The hypothesis that depression involves reduced activity at norepinephrine and serotonin synapses.

motivation
The set of factors that initiate, sustain, and direct behavior.

motor cortex
The area in the frontal lobes that controls voluntary (nonreflexive) body movements; the primary motor cortex is on the precentral gyrus.

motor neuron
A neuron that carries commands to the muscles and organs.

movement agnosia
Impairment of the ability to perceive movement.

MPOA
See *medial preoptic area*.

MRI
See *magnetic resonance imaging*.

Müllerian ducts
Early structures that in the female develop into the uterus, fallopian tubes, and inner vagina.

Müllerian inhibiting hormone
A hormone released in the male that causes the Müllerian ducts to degenerate.

multiple sclerosis (MS)
A motor disorder caused by the deterioration of myelin (demyelination) and neuron loss in the central nervous system.

muscle spindles
Receptors that detect stretching in muscles.

myasthenia gravis
A disorder of muscular weakness caused by reduced numbers or sensitivity of acetylcholine receptors.

myelin
A fatty tissue that wraps around an axon to insulate it from the surrounding fluid and from other neurons.

myelin stain
A staining method that stains the fatty insulation on axons, thus identifying neural pathways.

narcolepsy
A chronic neurological disorder in which individuals fall asleep suddenly during the daytime and go directly into REM sleep.

natural killer cell
A type of immune cell that attacks and destroys certain kinds of cancer cells and cells infected with viruses.

natural selection
The principle that those whose genes endow them with greater speed, intelligence, or health are more likely to survive and transmit their genes to more offspring.

nature versus nurture
The issue of the relative importance of heredity (nature) and environment (nurture).

negative color aftereffect
The experience of a color's complement following stimulation by the color.

negative symptoms
Aspects of schizophrenia characterized by the absence or insufficiency of normal behaviors, including lack of affect (emotion), inability to experience pleasure, lack of motivation, poverty of speech, and impaired attention.

neglect
A disorder in which the person ignores objects, people, and activity on the side opposite the brain damage.

nerve
A bundle of axons running together in the peripheral nervous system.

neural network
A group of neurons that function together to carry out a process.

neurofibrillary tangles

Abnormal accumulations of the protein tau that develop inside neurons and are associated with the death of brain cells in people with Alzheimer's disease and Down syndrome.

neurogenesis
The birth of new neurons.

neuroleptics
Drugs that block dopamine receptors in the brain, decreasing many of the positive symptoms of schizophrenia; they may cause tardive dyskinesia after prolonged use.

neuron
A specialized cell that conveys sensory information into the brain, carries out the operations involved in thought and feeling and action, or transmits commands out into the body to control muscles and organs; a single neural cell, in contrast to a *nerve*.

neuropeptide Y (NPY)
A transmitter released by NPY/AgRP neurons in the arcuate nucleus of the hypothalamus when nutrient levels diminish; it is a powerful stimulant for eating and conserves energy.

neurotoxin
A neuron poison; a substance that impairs the functioning of a neuron.

neurotransmitter
A chemical substance released by a neuron (usually at a synapse) that binds to receptors on the same neuron, nearby neurons, or other tissues such as muscles or organs.

neurotrophins
Chemicals that enhance development and survival in neurons.

nicotine
The primary psychoactive and addictive ingredient in tobacco.

Nissl stain
A staining method that stains cell bodies.

node of Ranvier
A gap in the myelin sheath covering an axon.

nondeclarative memory
Non-statable memories that result from procedural or skills learning, emotional learning, and simple conditioning.

nondecremental
A property of the action potential, which travels through the neuron without any decrease in size.

non-REM sleep
The periods of sleep that are not rapid eye movement sleep; Stages 1 through 4, characterized by reduced metabolic activity, slowed breathing and heart rate, and reduced dreaming.

NPY
See *neuropeptide Y*.

NPY/AgRP neurons
Neurons in the arcuate nucleus that release neuropeptide Y, agouti-related protein, and GABA, all of which initiate eating.

nucleus
(1) The part of every cell that contains the chromosomes and governs activity in the cell. (2) A group of neuron cell bodies in the central nervous system.

nucleus accumbens
A forebrain structure that is part of the mesolimbocortical dopamine system and a potent center for reward.

obesity gene
A gene on chromosome 6 that causes obesity; in mice, it results in an inability to produce leptin.

object agnosia
Impairment of the ability to recognize objects visually.

obsessive-compulsive disorder (OCD)
A disorder consisting of obsessions (recurring thoughts) and compulsions (repetitive, ritualistic acts the person feels compelled to perform).

occipital lobe

The most posterior part of each cerebral hemisphere and the location of the visual cortex.

OCD
See *obsessive-compulsive disorder*.

oligodendrocyte
A type of glial cell that forms the myelin covering of neurons in the brain and spinal cord.

opiate
Any drug derived from the opium poppy. The term is also used to refer to effects at opiate receptors, including those by endorphins.

opponent process theory
A color vision theory that attempts to explain color vision in terms of opposing neural processes.

optogenetics
Control of neurons by creating light-responsive ion channels in the cell membrane.

orexin
A neuropeptide released by lateral hypothalamic neurons that increases feeding and arousal; also known as *hypocretin*.

organizing effects
Hormonal effects of sexual development that occur during the prenatal period and shortly after birth and are permanent.

organ of Corti
The sound-analyzing structure on the basilar membrane of the cochlea; it consists of four rows of hair cells, their supporting cells, and the tectorial membrane.

organum vasculosum lamina terminalis (OVLT)
A structure bordering the third ventricle that monitors fluid content in the cells and contributes to the control of osmotic thirst.

osmotic thirst

Thirst that occurs when the fluid content is low inside the body's cells.

ossicles
Tiny bones in the middle ear that operate in lever fashion to transfer vibration from the tympanic membrane to the cochlea; they also produce a slight amplification of the sound.

outer hair cells
Three rows of about 12,000 cells located on the basilar membrane toward the outside of the cochlea's coil; they amplify the cochlea's output and sharpen frequency tuning, possibly by adjusting the tension of the tectorial membrane.

out-of-body experience
A phenomenon, usually resulting from brain damage or epilepsy, in which the person hallucinates seeing his or her detached body from another location, such as from a position above the body.

ovaries
The female gonads, where the ova develop.

OVLT
See *organum vasculosum lamina terminalis*.

oxytocin
A peptide hormone and neuropeptide transmitter involved in lactation, sexual arousal, and orgasm, as well as social recognition and bonding; sometimes called the "sociability molecule."

PAG
See *periaqueductal gray*.

parasympathetic nervous system
The branch of the autonomic nervous system that slows the activity of most organs to conserve energy and activates digestion to renew energy.

paraventricular nucleus (PVN)
A structure in the hypothalamus that regulates eating and metabolic processes such as body temperature, fat storage, and

cellular metabolism, largely controlled by inputs from the nucleus of the solitary tract.

parietal lobe
The part of each cerebral hemisphere located above the lateral fissure and between the central sulcus and the occipital lobe; it contains the somatosensory cortex and visual association areas.

Parkinson's disease
A movement disorder characterized by motor tremors, rigidity, loss of balance and coordination, and difficulty in moving, especially in initiating movements; caused by deterioration of the substantia nigra.

partial depolarization
A positive change in a neural membrane's voltage, which is excitatory and makes an action potential more likely to occur. See *excitatory postsynaptic potential* for the synaptic effect.

parvocellular system
A division of the visual system, extending from the retina through the visual association areas, that is specialized for fine detail and color.

peptide YY3-36 (PYY)
An appetite-suppressing peptide hormone released in the intestines in response to food.

perception
The interpretation of sensory information.

periaqueductal gray (PAG)
A brain stem structure with numerous endorphin synapses; stimulation reduces pain transmission at the spinal cord level. The PAG also produces symptoms of drug withdrawal.

peripheral nervous system (PNS)
The part of the nervous system made up of the cranial nerves and spinal nerves.

PET
See *positron emission tomography*.

PGO waves
Oscillations of excitation that flow from the pons through the lateral geniculate nucleus of the thalamus to the occipital area and appear to initiate the EEG desynchrony of REM sleep.

phantom pain
Pain that seems to be in a missing limb.

phenotype
In heredity, the characteristic of the individual.

phenylketonuria
An inherited form of intellectual disability in which the body fails to metabolize the amino acid phenylalanine, which interferes with myelination during development.

pheromones
Airborne chemicals released by an animal that have physiological or behavioral effects on another animal of the same species.

phonological hypothesis
The idea that the fundamental problem in dyslexia is impaired phoneme processing.

photopigments
Light-sensitive chemicals in the visual receptors that initiate the neural response.

phototherapy
A treatment for winter depression involving the use of high-intensity lights for a period of time each day.

phrenology
The theory in the early 1900s that “faculties” of emotion and intellect were located in precise areas of the brain and could be assessed by feeling bumps on the skull.

pineal gland
A gland located just posterior to the thalamus that secretes sleep-inducing melatonin; it controls seasonal cycles in nonhuman animals and participates with other structures in controlling daily rhythms in humans.

pinna
The ear flap on each side of the head; the outer ear.

pitch
The *experience* of the frequency of a sound.

place cells
Cells in the hippocampus that increase their firing rate when the individual is in a specific location in the environment.

place theory
A theory that states that the frequency of a sound is identified by the location of maximal vibration on the basilar membrane and which neurons are firing most.

plagiarism
The theft of or use without permission of another's work or ideas.

planum temporale
The area in each temporal lobe that is the location in the left hemisphere of Wernicke's area and that is larger on the left in most people.

plaques
Clumps of amyloid beta (Aβ), a type of protein, that cluster among axon terminals and interfere with neural transmission in the brains of people with Alzheimer's disease and Down syndrome.

plasticity
The ability to be modified; a characteristic of the nervous system.

PNS
See *peripheral nervous system*.

polarization
A difference in electrical charge between the inside and outside of a neuron.

polygenic
Determined by several genes rather than a single gene.

POMC neurons
See *proopiomelanocortin (POMC) neurons*.

pons
A part of the brain stem that contains centers related to sleep and arousal.

positive symptoms
Symptoms of schizophrenia that involve the presence or exaggeration of behaviors, such as delusions, hallucinations, thought disorder, and bizarre behavior.

positron emission tomography (PET)
An imaging technique that reveals function. It involves injecting a radioactive substance into the bloodstream, which is taken up by parts of the brain according to how active they are; the scanner makes an image that is color coded to show the relative amounts of activity.

posterior
Toward the rear.

posterior parietal cortex
An association area that brings together the body senses, vision, and audition. It determines the body's orientation in space, the location of the limbs, and the location in space of objects detected by touch, sight, and sound.

postsynaptic
A term referring to a neuron that receives transmission from another neuron.

posttraumatic stress disorder (PTSD)
A prolonged stress reaction to a traumatic event; typically characterized by recurrent thoughts and images (flashbacks), nightmares, lack of concentration, and overreactivity to environmental stimuli, such as loud noises.

precentral gyrus
The gyrus anterior to, and extending the length of, the central sulcus; the location of the primary motor cortex.

predatory aggression

Hostile or destructive behavior in which an animal attacks and kills its prey or a human engages in a premeditated, unprovoked, and similarly relatively emotionless attack.

prefrontal cortex
The most anterior cortex of the frontal lobes; involved in working memory, planning and organization of behavior, and regulation of behavior in response to its consequences. It also integrates information about the body with sensory information from the world to select and plan movements.

premotor cortex
An area anterior to the primary motor cortex that combines information from the prefrontal cortex and the posterior parietal cortex and begins the programming of a movement.

preoptic area
A structure in the hypothalamus that contains warmth-sensitive cells and cold-sensitive cells and participates in the control of body temperature. See *medial preoptic area* regarding regulation of sexual behavior.

presynaptic
A term referring to a neuron that transmits to another neuron.

presynaptic excitation
Increased release of neurotransmitter from a neuron's terminal as the result of another neuron's release of neurotransmitter onto the terminal (an axoaxonic synapse).

presynaptic inhibition
Decreased release of neurotransmitter from a neuron's terminal as the result of another neuron's release of neurotransmitter onto the terminal (an axoaxonic synapse).

prevalence
The total count or percentage of people with a condition at a specific point in time.

primary motor cortex
The area on the precentral gyrus responsible for the execution of voluntary movements.

primary somatosensory cortex
The first stage in the cortical-level processing of somatosensory information, which is processed through the four subareas of the primary somatosensory cortex and then passed on to the secondary somatosensory cortex.

proactive aggression
Unprovoked and emotionless hostile or violent behavior intended to result in gain for the aggressor, such as to intimidate, dominate, or rob the victim.

progesterone
A hormone produced in greater abundance in females, in whom it controls reproductive functions, including sexual receptivity and desire; in males, it is needed to produce testosterone.

proliferation
The first stage of nervous system development, in which cells that will become neurons multiply at the rate of 250,000 new cells every minute.

proopiomelanocortin (POMC) neurons
Cells in the arcuate nucleus that release the peptide proopiomelanocortin, a protein that activates satiety neurons and decreases eating.

proprioception
The sense that informs us about the position and movement of the parts of the body.

prosody
The use of intonation, emphasis, and rhythm to convey meaning in speech.

prosopagnosia
An impairment of the ability to visually recognize familiar faces.

psychedelic drug
Any compound that causes perceptual distortions in the user.

psychoactive drug
Any drug that has psychological effects, such as anxiety relief or hallucinations.

psychosis
A severe mental disturbance of reality, thought, and orientation.

psychosurgery
The use of surgical intervention to treat cognitive and emotional disorders.

PTSD
See *posttraumatic stress disorder*.

pure tone
A sound consisting of a single frequency.

PVN
See *paraventricular nucleus*.

PYY
See *peptide* $YY_{3\text{-}36}$.

radial glial cells
Specialized glial cells that provide a scaffold for most migrating neurons as they move perpendicularly from the ventricular surface to their final location.

rapid eye movement (REM) sleep
A stage of sleep characterized by darting horizontal eye movements, beta EEG, physiological arousal, and muscular paralysis; it is a period of memory consolidation and deletion, synaptic pruning, and increased dreaming.

rate law
A principle that the intensity of a stimulus is represented in an axon by the frequency of action potentials.

reactive aggression
Hostile or violent behavior resulting from a threat (real or imagined) to the individual, characterized by heightened emotionality.

receptive field
In vision, the area of the retina from which a cell in the visual system receives its input.

receptor
A cell, often a specialized neuron, that is suited by its structure and function to respond to a particular form of energy, such as sound.

recessive
A term referring to an allele that will have an influence only when it is paired with the same recessive allele on the other chromosome.

reflex
A simple, automatic movement in response to a sensory stimulus.

regeneration
The growth of severed axons; in mammals, it is limited to the peripheral nervous system.

relative refractory period
The period during which a neuron can be fired again following an action potential but only by an above-threshold stimulus.

REM
See *rapid eye movement sleep*.

REM sleep behavior disorder
A sleep disorder in which the person is physically active during REM sleep.

reorganization
A shift in neural connections that changes the function of an area of the brain.

reserve hypothesis
The hypothesis that individuals with greater cognitive or brain capacity are able to compensate for brain changes due to aging, brain damage, or disorders such as Alzheimer's.

resting potential
The difference in charge between the inside and outside of the membrane of a neuron at rest.

reticular formation

A collection of more than 90 nuclei running through the middle of the hindbrain and the midbrain with roles in sleep and arousal, attention, reflexes, and muscle tone.

retina
The structure at the rear of the eye, which is made up of light-sensitive receptor cells and the neural cells that are connected to them.

retinal disparity
A discrepancy in the location of an object's image on the two retinas; a cue to the distance of a focused object.

retinotopic map
A map of the retina in the visual cortex, which results from adjacent receptors in the retina activating adjacent cells in the visual cortex.

retrieval
The process of accessing stored memories.

retrograde amnesia
The inability to remember events prior to impairment.

reuptake
The process by which a neurotransmitter is taken back into the presynaptic terminals by transporters.

reward
The positive effect on a user from a drug, electrical stimulation of the brain (ESB), sex, food, warmth, and so on.

rhodopsin
The photopigment in rods that is sensitive to all wavelengths of visible light.

SAD
See *seasonal affective disorder*.

salience network
A cortical network that detects significant stimuli that require attention and switches between the resting default mode network and the goal-directed central executive network.

saltatory conduction
The flow of electricity down the axon in which action potentials jump from one node of Ranvier to the next.

satiety
Satisfaction of appetite.

scanning electron microscope
A microscope that forms a three-dimensional image of up to 2 to 3 million times magnification by capturing electrons emitted by tissue when it is bombarded by a beam of electrons.

schizophrenia
A disabling disorder characterized by perceptual, emotional, and intellectual deficits, loss of contact with reality, and an inability to function in life.

Schwann cell
A type of glial cell that forms the myelin covering on neurons outside the brain and spinal cord.

SCN
See *suprachiasmatic nucleus*.

SCR
See *skin conductance response*.

SDN
See *sexually dimorphic nucleus*.

seasonal affective disorder (SAD)
Depression that is seasonal, being more pronounced in the summer in some people and in the winter in others.

secondary somatosensory cortex
The part of the somatosensory cortex that receives information from the primary somatosensory cortex, from both sides of the body.

sedative
A calming effect of a drug.

sensation

The acquisition of sensory information.

sensory neuron
A neuron that carries information from the body and from the outside world into the central nervous system.

sensory-specific satiety
Decreased attractiveness of a food as the person or animal eats more of it.

set point
A value in a control system that is the system's point of equilibrium or homeostasis; departures from this value initiate actions to restore the set-point condition.

sex
The term for the biological characteristics that divide humans and other animals into the categories of male and female.

sexually dimorphic nucleus (SDN)
A part of the MPOA important to male sexual behavior. It is larger in male rats, and their level of sexual activity depends on SDN size.

SFO
See *subfornical organ*.

simple cell
A cell in the visual cortex that responds to a line or an edge that is at a specific orientation and a specific place on the retina.

skeletal muscles
The tissues that attach to bones and move the body and limbs.

skin conductance response (SCR)
A measure of sweat gland activation and thus sympathetic nervous system activity.

skin senses
Touch, warmth, cold, and pain (and, possibly, itch); the senses that arise from receptors in the skin.

slow-wave sleep

Stages 3 and 4 of sleep, characterized by delta EEG and increased body activity; it appears to be a period of brain recuperation and may play a role in consolidation of declarative memory.

smooth muscles
The tissues that control the contractions of internal organs other than the heart.

sodium-potassium pump
Large protein molecules that move sodium ions through the neuron membrane to the outside and potassium ions back inside, helping maintain the resting potential.

somatic nervous system
The division of the peripheral nervous system that carries sensory information into the central nervous system (CNS) and motor commands from the CNS to the skeletal muscles.

somatosensory cortex
The area in the parietal lobes that processes the skin senses and the senses that inform us about body position and movement, or proprioception; the primary somatosensory cortex is on the postcentral gyrus.

somatotopic map
The form of topographic organization in the motor cortex and somatosensory cortex, such that adjacent body parts are represented in adjacent areas of the cortex.

spatial frequency theory
The idea that visual cortical cells do a Fourier frequency analysis of the luminosity variations in a scene.

spatial summation
The process of combining potentials that occur simultaneously at different locations on the dendrites and cell body.

spinal cord
A part of the central nervous system; the spinal nerves, which communicate with the body below the head, enter and leave the spinal cord.

spinal nerves
The peripheral axonal bundles that enter and leave the spinal cord at each vertebra and communicate with the body below the head.

spontaneous confabulation
Fabrication of stories and facts to make up for those missing from memory.

stem cells
Undifferentiated cells that can develop into specialized cells, such as neurons, muscle, or blood.

stereotaxic instrument
A device used for the precise positioning in the brain of an electrode or other device, such as a cannula.

stimulant
A drug that activates the nervous system to produce arousal, increased alertness, and elevated mood.

stress
A condition in the environment that makes unusual demands on the organism, such as threat, failure, or bereavement; the individual's negative response to a stressful situation.

striatum
The caudate nucleus and putamen, both of the basal ganglia, and the nucleus accumbens.

stroke
A medical condition caused by a loss of blood flow in the brain (also known as *cerebrovascular accident*).

subfornical organ (SFO)
One of the structures bordering the third ventricle that increases drinking when stimulated by angiotensin II.

substance P
A neuropeptide involved in pain signaling.

substantia nigra

The nucleus that sends dopamine-releasing neurons to the striatum and that deteriorates in Parkinson's disease.

sudden cardiac death
A fatal event when stress causes excessive sympathetic activity that sends the heart into fibrillation, contracting so rapidly that little or no blood is pumped.

sulcus
A shallow groove or space between two *gyri*, not as deep as a *fissure*.

superior
Above another structure.

superior colliculi
The part of the tectum in the brain stem that is involved in visual functions, such as guiding eye movements and fixation of gaze.

supplementary motor area
The prefrontal area that assembles sequences of movements, such as those involved in eating or playing the piano, prior to execution by the primary motor cortex.

suprachiasmatic nucleus (SCN)
A structure in the hypothalamus that (1) was found to be larger in gay men than in heterosexual men, (2) regulates the reproductive cycle in female rats, and (3) is the main biological clock, controlling several activities of the circadian rhythm.

sympathetic ganglion chain
The structure running along each side of the spine through which most sympathetic neurons pass (and may synapse) on their way to and from the body's organs.

sympathetic nervous system
The branch of the autonomic nervous system that activates the body in ways that help it cope with demands, such as emotional stress and physical emergencies.

synapse
The structure in which a neuron passes electrical or chemical signals to another neuron, muscle, or organ.

synaptic cleft
The small gap between a presynaptic neuron and a postsynaptic neuron.

synesthesia
A condition in which stimulation in one sense triggers an experience in another sense, or a concept evokes an unrelated sensory experience.

tardive dyskinesia
Tremors and involuntary movements caused by blocking of dopamine receptors in the basal ganglia due to prolonged use of drugs that block dopamine signals.

TBI
See *traumatic brain injury*.

T cell
A type of leukocyte whose four types either attack invaders or help regulate the immune system.

tectorial membrane
A shelf-like membrane overlying the hair cells and the basilar membrane in the cochlea.

telephone theory
A theory of auditory frequency analysis, which stated that the auditory neurons transmit the actual sound frequencies to the cortex.

temporal lobe
The part of each cerebral hemisphere ventral to the lateral fissure; it contains the auditory cortex, visual and auditory association areas, Wernicke's area, and structures involved in learning and memory.

temporal summation
The process of combining potentials that arrive a short time apart on a neuron's dendrites and cell body.

terminal
See *axon terminal*.

testes
The male gonads that produce sperm.

testosterone
The major sex hormone in males; a member of the class of androgens.

thalamus
A forebrain structure lying just below the lateral ventricles, which receives information from all sensory systems except olfaction and relays it to the respective cortical projection areas. It has additional roles in movement, memory, and consciousness.

theory
A system of statements that integrate and interpret diverse observations to explain some phenomenon.

theory of mind
The ability to attribute mental states to oneself and to others.

third interstitial nucleus of the anterior hypothalamus (INAH3)
A nucleus found to be half as large in gay men and heterosexual women as in heterosexual men and similar in size in women and male-to-female transgender individuals.

TMS
See *transcranial magnetic stimulation*.

tolerance
After repeated drug use, the individual becomes less responsive and requires increasing amounts of a drug to produce the same results.

tonotopically organized
A term that means that neurons from adjacent receptor locations project to adjacent cells in the auditory cortex, forming a tonotopic map.

Tourette syndrome
A disorder characterized by motor and phonic (sound) tics.

tract
A bundle of axons in the central nervous system.

transcranial magnetic stimulation (TMS)
A noninvasive stimulation technique that uses a magnetic coil to induce a voltage in brain tissue.

transgender
The term for an individual whose gender identity differs from the sex assigned at birth; the person may dress and live as the other sex and may undergo surgery for sex reassignment. Also termed *transsexual*.

transsexual
See *transgender*.

transmission electron microscope
A magnification system that passes a beam of electrons through a thin slice of tissue onto a detector plate that connects to a computer monitor, forming an image magnified up to 50 million times.

traumatic brain injury (TBI)
An injury caused by an external mechanical force, such as a blow to the head, sudden acceleration or deceleration, or penetration.

trichromatic theory
The hypothesis that three color processes account for all the colors we are able to distinguish.

twin studies
A technique for studying the roles of heredity and environment by assessing how similar twins are in some characteristic; their similarity is compared with that of nontwin siblings, or the similarity between identical twins is compared with the similarity between fraternal twins.

tympanic membrane
The eardrum, a very thin membrane stretched across the end of the auditory canal; its vibration transmits sound energy to the ossicles.

ultradian rhythm
A rhythm with a length of less than a day, including the sleep stages and the basic rest and activity cycle during the day.

unipolar depression
See *major depressive disorder*.

ventral
Toward the stomach side.

ventral root
The branch of each spinal nerve through which the motor neurons exit.

ventral stream
The visual processing pathway that extends into the temporal lobes; it is especially concerned with the identification of objects.

ventral tegmental area
A part of the mesolimbocortical dopamine system, which sends neurons to the nucleus accumbens and is a potent reward area.

ventricles
Cavities in the brain filled with cerebrospinal fluid.

ventromedial hypothalamus (VMH)
An area in the hypothalamus important for female sexual receptivity and male mating vigor in rats. It is also involved in eating behavior, and destruction in rats produces extreme obesity.

vesicle
A membrane-enclosed container that stores neurotransmitter in the neuron terminal.

vestibular sense
The sense that helps us maintain balance and that provides information about head position and movement; the receptors are located in the vestibular organs.

visual acuity
The ability to distinguish visual details.

visual cortex
The part of each occipital lobe where visual information is processed.

visual field
The part of the environment that is being registered on the retina.

visual word form area (VWFA)
An area in the human inferior temporal lobe involved in reading words.

VNO
See *vomeronasal organ*.

volley theory
A hypothesis of auditory frequency analysis that states that groups of neurons follow the frequency of a sound when the frequency exceeds the firing rate capability of a single neuron.

voltage
The difference in electrical charge between two points.

vomeronasal organ (VNO)
A cluster of receptors in the nasal cavity that detect pheromones.

vulnerability
The idea that genes produce susceptibility to a disorder and that environmental challenges may combine with a person's biological susceptibility to exceed the threshold required to produce the disorder.

vulnerability model
The idea that environmental challenges combine with a person's genetic vulnerability for a disease to exceed the threshold for the disease.

VWFA
See *visual word form area*.

Wernicke's aphasia
Language impairment resulting from damage to Wernicke's area; the person has difficulty understanding and producing spoken and written language.

Wernicke's area

A brain area just posterior to the auditory cortex (in the left hemisphere in most people) that interprets spoken and written language input and generates spoken and written language.

winter birth effect
The tendency for more schizophrenics to be born during the winter and spring months than at any other time of the year.

Wisconsin Card Sorting Test
A test of prefrontal functioning that requires the individual to sort cards using one criterion and then change to another criterion.

withdrawal
A negative reaction that occurs when drug use is stopped.

Wolffian ducts
The early structures that in the male develop into the seminal vesicles and the vas deferens.

working memory
A form of short-term memory that provides a temporary "register" for information while it is being used.

X-linked
In heredity, a condition in which a gene on the X chromosome is not paired with a gene on the shorter Y chromosome, so that a single recessive gene is adequate to produce a characteristic.

zygote
A fertilized egg.

REFERENCES

aan het Rot, M., Collins, K. A., Murrough, J. W., Perez, A. M., Reich, D. L., Charney, D. S., et al. (2010). Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biological Psychiatry, 15, 139–145.

Abbott, A. (2019, August 21). Italian blindness researchers planning monkey studies threatened after health ministry releases names. Science News. Retrieved from https://www.sciencemag.org/news/2019/08/italian-blindness-researchers-planning-monkey-studies-threatened-after-health-ministry

Abe, K., Kroning, J., Greer, M. A., & Critchlow, V. (1979). Effects of destruction of the suprachiasmatic nuclei on the circadian rhythms in plasma corticosterone, body temperature, feeding and plasma thyrotropin. Neuroendocrinology, 29, 119–131.

Abelson, J. F., Kwan, K. Y., O'Roak, B. J., Baek, D. Y., Stillman, A. A., Morgan, T. M., et al. (2005). Sequence variants in *SLITRK1* are associated with Tourette's syndrome. Science, 319, 317–320.

Abrahams, B. S., & Geschwind, D. H. (2008). Advances in autism genetics: On the threshold of a new neurobiology. Nature Reviews Genetics, 9, 341–355.

Abramowitz, J. S., Taylor, S., & McKay, D. (2009). Obsessive-compulsive disorder. Lancet, 374, 491–499.

Adams, D. B., Gold, A. R., & Burt, A. D. (1978). Rise in female-initiated sexual activity at ovulation and its suppression by oral contraceptives. New England Journal of Medicine, 299, 1145–1150.

Adler, L. E., Olincy, A., Cawthra, E. M., McRae, K. A., Harris, J. G., Nagamoto, H. T., et al. (2004). Varied effects of atypical neuroleptics on P50 auditory gating in schizophrenia patients. American Journal of Psychiatry, 161, 1822–1828.

Adolphs, R., Tranel, D., & Damasio, A. R. (1998). The human amygdala in social judgment. Nature, 393, 470–474.

Adrien, J. (2002). Neurobiological bases for the relation between sleep and depression. Sleep Medicine Reviews, 6, 341–351.

Advokat, C. D., Comaty, J. E., & Julien, R. M. (2018). Julien's primer of drug action (14th ed.). New York, NY: Worth.

Agnew-Blais, J. C., Polanczyk, G. V., Danese, A., Wertz, J., Moffitt, T. E., & Arseneault, L. (2016). Evaluation of the persistence, remission, and emergence of attention-deficit/hyperactivity disorder in young adulthood. JAMA Psychiatry, 73, 713–720.

Ahorukomeye, P., Disotuar, M. M., Gajewiak, J., Karanth, S., Watkins, M., Robinson, S. D., et al. (2019). Fish-hunting cone snail venoms are a rich source of minimized ligands of the vertebrate insulin receptor. eLIFE. doi:10.7554/eLife.41574.

Ainsworth, C. (2009). Full without food: Can surgery cure obesity? New Scientist, September 2. Retrieved from www.newscientist.com/article/mg20327241.100-full-without-food-can-surgerycure-obesity.html

Akbarian, S., Bunney, W. E., Potkin, S. G., Wigal, S. B., Hagman, J. O., Sandman, C. A., et al. (1993). Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development. Archives of General Psychiatry, 50, 169–177.

Akbarian, S., Viñuela, A., Kim, J. J., Potkin, S. G., Bunney, W. E., & Jones, E. G. (1993). Distorted distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase neurons in temporal lobe of schizophrenics implies anomalous cortical development. Archives of General Psychiatry, 50, 178–187.

Akeju, O., Loggia, M. L., Catana, C., Pavone, K. J., Vazquez, R., Rhee, J., et al. (2014). Disruption of thalamic functional connectivity is a neural correlate of dexmedetomidine-induced unconsciousness. eLife, 3(e04499). doi:10.7554/eLife.04499

Akheruzzaman, M., Hegde, V., & Dhurandhar, N. V. (2018). Twenty-five years of research about adipogenic adenoviruses: a systematic review. Obesity Reviews, 20, 499–509.

Alain, C., Arnott, S. R., Hevenor, S., Graham, S., & Grady, C. L. (2001). “What” and “where” in the human auditory system. Proceedings of the National Academy of Sciences, 98, 12301–12306.

Alaska Oil Spill Commission. (1990, February). Final report: Details about the accident. Retrieved from https://www.evostc.state.ak.us/facts/details.cfm

Alberini, C., & LeDoux, J. E. (2013). Memory consolidation. Current Biology, 23(17), R746–750. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24028957

Albert, D. J., Walsh, M. L., Gorzalka, B. B., Siemens, Y., & Louie, H. (1986). Testosterone removal in rats results in a decrease in social aggression and a loss of social dominance. Physiology and Behavior, 36, 401–407.

Albrecht, D. G., De Valois, R. L., & Thorell, L. G. (1980). Visual cortical neurons: Are bars or gratings the optimal stimuli? Science, 207, 88–90.

Alexander, C. N., Langer, E. J., Newman, R. I., Chandler, H. M., & Davies, J. L. (1989). Transcendental meditation, mindfulness, and longevity: An experimental study with the elderly. Journal of Personality and Social Psychology, 57, 950–964.

Alexander, G. E., & Crutcher, M. D. (1990). Preparation for movement: Neural representations of intended direction in three motor areas of the monkey. Journal of Neurophysiology, 64, 133–150.

Alexander-Bloch, A. F., Reiss, P. T., Rapoport, J., McAdams, H., Giedd, J. N., Bullmore, E. T., et al. (2014). Abnormal cortical growth in schizophrenia targets normative modules of synchronized development. Biological Psychiatry, 76, 438–446.

Alexandrov, L. B., Ju, Y. S., Haase, K., Van Loo, P., Martincorena, I., Ni-Zainal, S., et al. (2016). Mutational signatures associated with tobacco smoking in human cancer. Science, 354, 618–622.

Aleyasin, H., Flanigan, M., & Russo, S. J. (2018). Neurocircuitry of aggression and aggression seeking behavior: Nose poking into brain circuitry controlling aggression. Current Opinion in Neurobiology, 49, 184–192.

Alkire, M. T., Haier, R. J., Fallon, J. H., & Cahill, L. (1998). Hippocampal, but not amygdala, activity at encoding correlates with long-term free recall of nonemotional information. Proceedings of the National Academy of Sciences, 95, 14506–14510.

Allegretta, M., Nicklas, J. A., Sriram, S., & Albertini, R. J. (1990). T cells responsive to myelin basic protein in patients with multiple sclerosis. Science, 247, 718–721.

Alliance for Regenerative Medicine. (2015a). The Alliance for Regenerative Medicine issues position statement regarding

human embryo germline genome editing. Retrieved from http://alliancerm.org/press/alliance-regenerative-medicine-issues-position-statement-regarding-human-embryo-germline

Alliance for Regenerative Medicine. (2015b). Gene-editing summit supports some research in human embryos. Retrieved from http://alliancerm.org/news/gene-editing-summit-supports-some-research-human-embryos

Allison, T., & Cicchetti, D. V. (1976). Sleep in mammals: Ecological and constitutional correlates. Science, 194, 732–734.

Almeida, D. M., Jandacek, R. J., Weber, W. A., & McNamara, R. K. (2016). Docosahexaenoic acid biostatus is associated with event-related functional connectivity in cortical attention networks of typically developing children. Nutritional Neuroscience, 20, 246–254.

Altar, C. A., Laeng, P., Jurata, L. W., Brockman, J. A., Lemire, A., Bullard, J., et al. (2004). Electroconvulsive seizures regulate gene expression of distinct neurotrophic signaling pathways. Journal of Neuroscience, 24, 2667–2677.

Altena, E., Vrenken, H., Van Der Werf, Y. D., van den Heuvel, O. A., & Van Someren, E. J. W. (2010). Reduced orbitofrontal and parietal gray matter in chronic insomnia: A voxel-based morphometric study. Biological Psychiatry, 67, 182–185.

Alzheimer's Association. (2020). 2020 Alzheimer's disease facts and figures. Retrieved from https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf

Alzheimer's Association. (n.d.-a). FDA-approved treatments for Alzheimer's. Retrieved from

https://www.alz.org/media/documents/fda-approved-treatments-alzheimers-ts.pdf

Alzheimer's Association (n.d.-b). Types of dementia. Retrieved from https://www.alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia

Amad, A., Ramoz, N., Thomas, P., Jardri, R., & Gorwood, P. (2014). Genetics of borderline personality disorder: Systematic review and proposal of an integrative model. Neuroscience and Biobehavioral Reviews, 40, 6–19.

Amano, M., Amiya, N., Takaoka, M., Sato, H., Tatani, T., Arakawa, O., & Sakakura, Y. (2019). Tetrodotoxin functions as a stress relieving substance in juvenile puffer Takifugu rubripes. Toxicon, 171, 54–61.

Amanzio, M., Pollo, A., Maggi, G., & Benedetti, F. (2001). Response variability to analgesics: A role for non-specific activation of endogenous opioids. Pain, 90, 205–215.

Ameis, S. H., Lerch, J. P., Taylor, M. J., Lee, W., Viviano, J. D., Pipitone, J., et al. (2016). A diffusion tensor imaging study in children with ADHD, autism spectrum disorder, OCD, and matched controls: Distinct and non-distinct white matter disruption and dimensional brain-behavior relationships. American Journal of Psychiatry, 173, 1213–1222.

American Academy of Sleep Medicine. (2010, June 7). "Sexsomnia" is common in sleep center patients, study finds. Science Daily. Retrieved from https://www.sciencedaily.com/releases/2010/06/100607065547.htm

American Medical Association. (1992). Use of animals in biomedical research: The challenge and response. Chicago, IL: Author.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC: Author.

American Psychological Association. (2017). Ethical principles of psychologists and code of conduct. Retrieved from https://www.apa.org/ethics/code/

Amin, N. D., & Paşca, S. P. (2018). Building models of brain disorders with three-dimensional organoids. Neuron, 100, 389–405.

Amrollahi, Z., Rezaei, F., Salehi, B., Modabbernia, A.-H., Maroufi, A., Esfandiari, G.-R., et al. (2011). Double-blind, randomized placebo-controlled 6-week study on the efficacy and safety of the tamoxifen adjunctive to lithium in acute bipolar mania. Journal of Affective Disorders, 129, 327–331.

Anaclet, C., Ferrari, L., Arrigoni, E., Bass, C. E., Saper, C. B., Lu, J., & Fuller, P. M. (2014). The GABAergic parafacial zone is a medullary slow wave sleep-promoting center. Nature Neuroscience, 17, 1217–1224.

Anagnostou, E., Soorya, L., Brian, J., Dupuis, A., Mankad, D., Smile, S., & Jacob, S. (2014). Intranasal oxytocin in the treatment of autism spectrum disorders: A review of literature and early safety and efficacy data in youth. Brain Research. doi:10.1016/j.brainres.2014.01.049

Anderman, M. L., & Lowell, B. B. (2017). Toward a wiring diagram understanding of appetite control. Neuron, 95, 757–778.

Anders, T. F., & Roffwarg, H. P. (1973). The effects of selective interruption and deprivation of sleep in the human newborn. Developmental Psychobiology, 6, 79–91.

Andersen, S., & Skorpen, F. (2009). Variation in the COMT gene: Implications for pain perception and pain treatment. Summary Pharmacogenomics, 10, 669–684.

Anderson, A. K., & Phelps, E. A. (2001). Lesions of the human amygdala impair enhanced perception of emotionally salient events. Nature, 411, 305–309.

Anderson, B., & Harvey, T. (1996). Alterations in cortical thickness and neuronal density in the frontal cortex of Albert Einstein. Neuroscience Letters, 210, 161–164.

Anderson, M., & Hanse, E. (2010). Astrocytes impose postburst depression of release probability at hippocampal glutamate synapses. Journal of Neuroscience, 30, 5776–5780.

Anderson, P. (2019). Aducanumab about-face: Experts weigh in. Medscape Psychiatry. Retrieved from https://www.medscape.com/viewarticle/920946

Anderson, S. W., Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1999). Impairment of social and moral behavior related to early damage in human prefrontal cortex. Nature Neuroscience, 2, 1032–1037.

Ando, J., Ono, Y., & Wright, M. J. (2001). Genetic structure of spatial and verbal working memory. Behavior Genetics, 31, 615–624.

Ando, K., Laborde, Q., Lazar, A., Godefroy, D., Youssef, I., Amar, M., et al. (2014). Inside Alzheimer brain with CLARITY: Senile plaques, neurofibrillary tangles and axons in 3-D. Acta Neuropathology, 128, 457–459.

Andolfatto, P. (2005). Adaptive evolution of non-coding DNA in Drosophila. Nature, 437, 1149–1152.

Andrade, J. (1995). Learning during anaesthesia: A review. British Journal of Psychology, 86, 479–506.

Andreani, T. S., Itoh, T. Q., Yildirim, E., Hwangbo, D.-S., & Allada, R. (2015). Genetics of circadian rhythms. Sleep Medicine Clinics, 10, 413–421.

Andreano, J. M., & Cahill, L. (2009). Sex influences on the neurobiology of learning and memory. Learning and Memory, 16, 248–266.

Andreasen, N. C. (1984). The broken brain. New York, NY: Harper & Row.

Andreasen, N. C., Flaum, M., Swayze, V. W., II, Tyrrell, G., & Arndt, S. (1990). Positive and negative symptoms in schizophrenia: A critical reappraisal. Archives of General Psychiatry, 47, 615–621.

Andreasen, N. C., Rezai, K., Alliger, R., Swayzee, V. W., II, Flaum, M., Kirchner, P., et al. (1992). Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia: Assessment with xenon 133 single-photon emission computed tomography and the Tower of London. Archives of General Psychiatry, 49, 943–958.

Andrews-Hanna, J. R., Snyder, A. Z., Vincent, J. L., Lustig, C., Head, D., Raichle, M. E., et al. (2007). Disruption of large-scale brain systems in advanced aging. Neuron, 56, 924–935.

Anguera, J. A., Boccanfuso, J., Rintoul, J. L., Al-Hashimi, O., Faraji, F., Janowich, J., et al. (2013). Video game training enhances cognitive control in older adults. Nature, 501, 97–103.

Annese, J., Schenker-Ahmed, N. M., Bartsch, H., Maechler, P., Sheh, C., Thomas, N., et al. (2014). Postmortem examination of

patient H.M.’s brain based on histological sectioning and digital 3D reconstruction. Nature Communications, 5, 3122. doi:10.1038/ncomms4122

Anonymous. (1970). Effects of sexual activity on beard growth in man. Nature, 226, 869–870.

Anson, P. (2020, January 15). Opioid of the future abandoned. Pain News Network. Retrieved from https://www.painnewsnetwork.org/stories/2020/1/15/opioid-of-the-future-abandoned

Anthony, J. C., Warner, L. A., & Kessler, R. C. (1994). Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the national comorbidity survey. Experimental and Clinical Psychopharmacology, 2, 244–268.

Antilla, S. A., & Leinonen, E. V. (2001). A review of the pharmacological and clinical profile of mirtazapine. CNS Drug Reviews, 7, 249–264.

Aoki, Y., Yoncheva, Y. N., Chen, B., Nath, T., Sharp, D., Lazar, M., et al. (2017). Association of white matter structure with autism spectrum disorder and attention-deficit/hyperactivity disorder. JAMA Psychiatry, 74, 1120–1128.

Aoki, Y., Yahata, N., Watanabe, T., Takano, Y., Kawakubo, Y., Kuwabara, H., et al. (2014). Oxytocin improves behavioural and neural deficits in inferring others’ social emotions in autism. Brain, 137, 3073–3086.

Apkarian, A. V., Sosa, Y., Krauss, B. R., Thomas, S. P., Fredrickson, B. E., Levy, R. E., et al. (2004). Chronic pain patients are impaired on an emotional decision-making task. Pain, 108, 129–136.

Arbib, M. A. (2005). From monkey-like action recognition to human language: An evolutionary framework for neurolinguistics. Behavioral and Brain Sciences, 28, 105–167.

Archer, J. (1991). The influence of testosterone on human aggression. British Journal of Psychology, 82, 1–28.

Archer, J., Graham-Kevan, N., & Davies, M. (2005). Testosterone and aggression: A reanalysis of Book, Starzyk, and Quinsey's (2001) study. Aggression and Violent Behavior, 10, 241–261.

Archer, S. N., Robillant, D. I., Shane, D. J., Smits, M., Williams, A., Arendt, J., et al. (2003). A length polymorphism in the circadian clock gene *Per3* is linked to delayed sleep phase syndrome and extreme diurnal preference. Sleep, 26, 413–415.

Argiolas, A., & Melis, M. R. (2004). The role of oxytocin and the paraventricular nucleus in the sexual behavior of male mammals. Physiology and Behavior, 83, 309–317.

Arnold, P. D., & Richter, M. A. (2001). Is obsessive-compulsive disorder an autoimmune disease? Canadian Medical Association Journal, 165, 1353–1358.

Arnold, P. E., Zai, G., & Richter, M. A. (2004). Genetics of anxiety disorders. Current Psychiatry Reports, 6, 243–254.

Arnone, D., McIntosh, A. M., Ebmeier, K. P., Munafò, M. R., & Anderson, I. M. (2012). Magnetic resonance imaging studies in unipolar depression: Systematic review and meta-regression analyses. European Neuropsychopharmacology, 22, 1–16.

Arsenault, P., Chiche, D., Brown, W., Miller, J., Treister, R., Leff, R., et al. (2018). NEO6860, modality-selective TRPV1 antagonist: A

randomized, controlled, proof-of-concept trial in patients with osteoarthritis knee pain. Pain Reports, 3, e696.

Arzy, S., Seeck, M., Ortigue, S., Spinelli, L., & Blanke, O. (2006). Induction of an illusory shadow person. Nature, 443(287), 287.

Asai, M., Ramachandrappa, S., Joachim, M., Shen, Y., Zhang, R., Nuthalapati, N., et al. (2013). Loss of function of the melanocortin 2 receptor accessory protein 2 is associated with mammalian obesity. Science, 341, 275–278.

Aschoff, J. (1984). Circadian timing. Annals of the New York Academy of Sciences, 423, 442–468.

Asher, J. E., Lamb, J. A., Brocklebank, D., Cazier, J. B., Maestrini, E., Addis, L., et al. (2009). A whole-genome scan and fine-mapping linkage study of auditory-visual synesthesia reveals evidence of linkage to chromosomes 2q24, 5q33, 6p12, and 12p12. American Journal of Human Genetics, 84, 279–285.

Ashour, M. H., Jain, S. K., Kattan, K. M., al-Daeef, A. Q., Abdal-Jabbar, M. S., al-Tahan, A. R., et al. (1995). Maximal thymectomy for myasthenia gravis. European Journal of Cardio-thoracic Surgery, 9, 461–464.

Ashtari, M., Avants, B., Cyckowski, L., Cervellione, K. L., Roofeh, D., Cook, P., et al. (2011). Medial temporal structures and memory functions in adolescents with heavy cannabis use. Journal of Psychiatric Research, 45, 1055–1066.

Asplund, C. L., Todd, J. J., Snyder, A. P., & Marois, R. (2010). A central role for the lateral prefrontal cortex in goal-directed and stimulus-driven attention. Nature Neuroscience, 13, 507–512.

Associated Press. (2019, March 26). Purdue Pharma, maker of OxyContin, settles lawsuit in Oklahoma. Retrieved from https://www.statnews.com/2019/03/26/purdue-pharma-maker-of-oxycontin-settles-opioids-lawsuit-in-oklahoma

Atkins, H. L., Bowman, M., Allan, D., Anstee, G., Arnold, D. L., Bar-Or, A., et al. (2016). Immunoablation and autologous naemopoietic stem-cell transplantation for aggressive multiple sclerosis: A multicenter group phase 2 trial. Lancet, 388, 576–585.

Augustine, V., Gokce, S. K., Lee, S., Wang, B., Davidson, T. J., Reimann, F., et al. (2018). Hierarchical neural architecture underlying thirst regulation. Nature, 555, 204–209.

Avidan, G., & Behrmann, M. (2009). Functional MRI reveals compromised neural integrity of the face processing network in congenital prosopagnosia. Current Biology, 19, 1146–1150.

Ax, A. (1953). The physiological differentiation between fear and anger in humans. Psychosomatic Medicine, 15, 433–442.

Axelsson, J., Sabra, S., Rylander, L., Rignell-Hydbom, A., Lindh, C. H., & Giwercman, A. (2018). Association between paternal smoking at the time of pregnancy and the semen quality in sons. PloS One, 13(11), e0107221. doi:10.1371/journal.pone.0207221

Azevedo, F. A. C., Carvalho, L. R. B., Grinberg, L. T., Farfel, J. M., Ferretti, R. E. L., Leite, R. E. P., et al. (2009). Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. Journal of Comparative Neurology, 513, 532–541.

Baaré, W. F. C., Holshoff Pol, H. E.., Boomsma, D. I., Posthuma, D., de Geus, E. J. C., Schnack, H. G., et al. (2001). Quantitative genetic modeling of variation in human brain morhpology. Cerebral Cortex, 11, 816–824.

Baars, B. J. (2005). Global workspace theory of consciousness: Toward a cognitive neuroscience of human experience. In S. Laureys (Ed.), The boundaries of consciousness: Neurobiology and neuropathology (pp. 45–54). New York, NY: Elsevier.

Babb, S., Malarcher, A., Schauer, G., Asman, K., & Jamal, A. (2017). Quitting smoking among adults—United States, 2000–2015. Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report, 65, 1457–1464.

Bach, A. C., Clausen, B. H., Möller, M., Vestergaard, B., Chi, C. N., Round, A., et al. (2012). A high-affinity, dimeric inhibitor of PSD-95 bivalently interacts with PDZ1-2 and protects against ischemic brain damage. Proceedings of the National Academy of Sciences, 109, 3317–3322.

Bach-y-Rita, P. (1990). Brain plasticity as a basis for recovery of function in humans. Neuropsychologia, 28, 547–554.

Bai, D., Yip, B. H. K., Windham,, G. C., Sourander, A., Francis, R., Yoffe, R., et al. (2019). Association of genetic and environmental factors with autism in a 5-country cohort. JAMA Psychiatry, 76, 1035–1043.

Bailer, U. F., Frank, G. K., Price, J. C., Meltzer, C. C., Becker, C., Mathis, C. A., et al. (2013). Interaction between serotonin transporter and dopamine D2/D3 receptor radioligand measures is associated with harm avoidant symptoms in anorexia and bulimia nervosa. Psychiatry Research: Neuroimaging, 211, 160–168.

Bailer, U. F., & Kaye, W. H. (2010, September 11). Serotonin: Imaging findings in eating disorders. In R. A. H. Adan & W. H. Kaye (Eds.), Behavioral neurobiology of eating disorders (pp. 59–78). Retrieved from http://eatingdisorders.ucsd.edu/research/pub/imaging/doc/2011/BailerKaye2011_PMID21243470.pdf

Bailer, U. F., Narendran, R., Frankle, W. G., Himes, M. L., Duvvuri, V., Mathis, C. A., & Kaye, W. H. (2012). Amphetamine induced dopamine release increases anxiety in individuals recovered from anorexia nervosa. International Journal of Eating Disorders, 45, 263–271.

Bailey, A., Le Couteur, A., Gottesman, I., Bolton, P., Simonoff, E., Yuzda, E., et al. (1995). Autism as a strongly genetic disorder: Evidence from a British twin study. Psychological Medicine, 25, 63–77.

Bailey, C. H., Bartsch, D., & Kandel, E. R. (1996). Toward a molecular definition of long-term memory storage. Proceedings of the National Academy of Sciences, 93, 13445–13452.

Bailey, J. M., & Bell, A. P. (1993). Familiality of female and male homosexuality. Behavior Genetics, 23, 313–322.

Bailey, J. M., & Benishay, D. S. (1993). Familial aggregation of female sexual orientation. American Journal of Psychiatry, 150, 272–277.

Bailey, J. M., Dunne, M. P., & Martin, N. G. (2000). Genetic and environmental influences on sexual orientation and its correlates in an Australian twin sample. Journal of Personality and Social Psychology, 78, 524–536.

Bailey, J. M., & Pillard, R. C. (1991). A genetic study of male sexual orientation. Archives of General Psychiatry, 48, 1089–1096.

Bailey, J. M., Pillard, R. C., Neale, M. C., & Agyei, Y. (1993). Heritable factors influence sexual orientation in women. Archives of General Psychiatry, 50, 217–223.

Baizer, J. S., Ungerleider, L. G., & Desimone, R. (1991). Organization of visual inputs to the inferior temporal and posterior parietal cortex in macaques. Journal of Neuroscience, 11, 168–190.

Baker, C. K., & Flannery, J. G. (2018). Innovative optogenetic strategies for vision restoration. Frontiers in Cellular Neuroscience, 12, Article 316. Retrieved from https://www.frontiersin.org/articles/10.3389/fncel.2018.00316/full

Bakker, J., Honda, S.-I., Harada, N., & Balthazart, J. (2002). The aromatase knock-out mouse provides new evidence that estradiol is required during development in the female for the expression of sociosexual behaviors in adulthood. Journal of Neuroscience, 22, 9104–9112.

Bakker, J., Honda, S.-I., Harada, N., & Balthazart, J. (2003). The aromatase knock-out (ArKO) mouse provides new evidence that estrogens are required for the development of the female brain. Annals of the New York Academy of Sciences, 1007, 251–262.

Baliki, M. N., Chialvo, D. R., Geha, P. Y., Levy, R. M., Harden, R. N., Parrish, T. B., et al. (2006). Chronic pain and the emotional brain: Specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. Journal of Neuroscience, 26, 12165–12173.

Baliki, M. N., Petre, B., Torbey, S., Herrmann, K. M., Huang, L., Schnitzer, T. J., et al. (2012). Corticostriatal functional connectivity predicts transition to chronic back pain. Nature Neuroscience, 15, 1117–1119.

Band, L. C., & Hull, E. M. (1990). Morphine and dynorphin(1-13) microinjected into the medial preoptic area and nucleus accumbens effects on sexual behavior in male rats. Brain Research, 524, 77–84.

Bao, A.-M., & Swaab, D. F. (2011). Sexual differentiation of the human brain: Relation to gender identity, sexual orientation and neuropsychiatric disorders. Frontiers in Neuroendocrinology, 32, 214–226.

Barbey, A. K. (2018). Network neuroscience theory of human intelligence. Trends in Cognitive Sciences, 22, 8–20.

Barinaga, M. (1996). Guiding neurons to the cortex. Science, 274, 1100–1101.

Barinaga, M. (1997). New imaging methods provide a better view into the brain. Science, 276, 1974–1981.

Barkley, R. A., Fischer, M., Smallish, L., & Fletcher, K. (2003). Does the treatment of attention-deficit/hyperactivity disorder with stimulants contribute to drug use/abuse? A 13-year prospective study. Pediatrics, 111, 97–109.

Barlassina, L., & Newen, A. (2013). The role of bodily perception in emotion: In defense of an impure somatic theory. Philosophy and Phenomenological Research. doi:10.1111/phpr.12041

Baro, M. (2019, October 23). Department of Defense awards FIU biomedical engineering team $6 million to expand testing of pioneering prosthetic hand system. FIU News. Retrieved from https://news.fiu.edu/2019/department-of-defense-awards-fiu-biomedical-engineering-team-6-million-to-expand-testing-of-pioneering-prosthetic-hand-system

Barres, R., Kirchner, H., Rasmussen, M., Yan, J., Kantor, F. R., Krook, A., et al. (2013). Weight loss after gastric bypass surgery in human obesity remodels promoter methylation. Cell Reports, 3, 1020–1027.

Bartlett, D. L., & Steele, J. B. (1979). Empire: The life, legend, and madness of Howard Hughes. New York, NY: Norton.

Bartlett, E. L., Sadagopan, S., & Wang, X. (2011). Fine frequency tuning in monkey auditory cortex and thalamus. Journal of Neurophysiology, 106, 849–859.

Barysheva, M., Jahanshad, N., Foland-Ross, L., Altshuler, L. L., & Thompson, P. M. (2013). White matter microstructural abnormalities in bipolar disorder: A whole brain diffusion tensor imaging study. Neuroimage: Clinical, 2, 558–568.

Basbaum, A. I., Bautista, D. M., Scherrer, G., & Julius, D. (2009). Cellular and molecular mechanisms of pain. Cell, 139, 267–284.

Basbaum, A. I., & Fields, H. L. (1984). Endogenous pain control systems: Brainstem spinal pathways and endorphin circuitry. Annual Review of Neuroscience, 7, 309–338.

Basbaum, A. I., & Jessell, T. M. (2013). Pain. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), Principles of neural science (5th ed., pp. 530–555). New York, NY: McGraw-Hill.

Bassett, M. (2019, March 11). Recent developments in hemophilia: Gene therapy. MedPage Today. Retrieved from https://www.medpagetoday.com/recent-developments/hemophilia/78500

Bastiaansen, J. A. C.J., Thioux, M., & Keysers, C. (2009). Evidence for mirror systems in emotions. Philosophical Transactions of the Royal Society B, 364, 2391–2404.

Bathelt, J., Scerif, G., Nobre, K., & Astle, D. (2019). Whole-brain white matter organization, intelligence, and educational

attainment. Trends in Neuroscience and Education, 15, 38–47.

Batista, A. P., Buneo, C. A., Snyder, L. H., & Andersen, R. A. (1999). Reach plans in eye-centered coordinates. Science, 285, 257–260.

Batterham, R. L., Cowley, M. A., Small, C. J., Herzog, H., Cohen, M. A., Dakin, C. L., et al. (2002). Gut hormone PYY3–36 physiologically inhibits food intake. Nature, 418, 650–654.

Bauer, G., Elsallab, M., & Abou-El-Enein, M. (2018). Concise review: A comprehensive analysis of reported adverse events in patients receiving unproven stem cell-based interventions. Stem Cells Translational Medicine, 7, 676–685.

Bauer, R. M. (1984). Autonomic recognition of names and faces in prosopagnosia: A neuropsychological application of the guilty knowledge test. Neuropsychologia, 22, 457–469.

Baulac, S., Huberfeld, G., Gourinkel-An, I., Mitropoulou, G., Beranger, A., Prud'homme, J.-F., et al. (2001). First genetic evidence of GABAA receptor dysfunction in epilepsy: A mutation in the γ2-subunit gene. Nature Genetics, 28, 46–48.

Baum, A., Gatchel, R. J., & Schaeffer, M. A. (1983). Emotional, behavioral, and physiological effects of chronic stress at Three Mile Island. Journal of Consulting and Clinical Psychology, 51, 565–572.

Baumann, M. H. (2014). Awash in a sea of "bath salts": Implications for biomedical research and public health. Addiction, 109, 1577–1579.

Baumeister, J.-C., Papa, G., & Foroni, F. (2016). Deeper than skin deep: The effect of botulinum toxin-A on emotion processing. Toxicon, 118, 86–90.

Baumgart, M., Snyder, H. M., Carrillo, M. C., Fazio, S., Kim, H., & Johns, H. (2015). Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimer's & Dementia, 11, 718–726.

Baumgartner, L. S., Moore, E., Shook, D., Messina, S., Day, M. C., Green, J., et al. (2018). Safety of autologous umbilical cord blood therapy for acquired sensorineural hearing loss in children. Journal of Audiology and Otology, 22, 209–222.

Baumgartner, N. (2017). Intersex parenting: Ethical and legal implications of the treatment of intersex infants and the ramifications for their families. Women Leading Change, 1(3). Retrieved from https://journals.tulane.edu/ncs/issue/view/22

Baumgartner, T., Heinrichs, M., Vonlanthen, A., Fischbacher, U., & Fehr, E. (2008). Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. Neuron, 58, 639–650.

Baxter, L. R., Phelps, M. E., Mazziotta, J. C., Guze, B. H., Schwartz, J. M., & Selin, C. E. (1987). Local cerebral glucose metabolic rates in obsessive-compulsive disorder. Archives of General Psychiatry, 44, 211–218.

Baxter, L. R., Phelps, M. E., Mazziotta, J. C., Schwartz, J. M., Gerner, R. H., Selin, C. E., et al. (1985). Cerebral metabolic rates for glucose in mood disorders: Studies with positron emission tomography and fluorodeoxyglucose F 18. Archives of General Psychiatry, 42, 441–447.

Baxter, L. R., Schwartz, J. M., Phelps, M. E., Mazziotta, J. C., Guze, B. H., Selin, C. E., et al. (1989). Reduction of prefrontal cortex glucose metabolism common to three types of depression. Archives of General Psychiatry, 46, 243–250.

Bayley, P. J., Hopkins, R. O., & Squire, L. R. (2006). The fate of old memories after medial temporal lobe damage. Journal of Neuroscience, 26, 13311–13317.

Beal, M. A., Yauk, C. L., & Marchetti, F. (2017). From sperm to offspring: Assessing the heritable genetic consequences of paternal smoking and potential public health impacts. Mutation Research, 773, 26–50.

Bechara, A., Damasio, H., Damasio, A. R., & Lee, G. P. (1999). Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. Journal of Neuroscience, 19, 5473–5481.

Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1997). Deciding advantageously before knowing the advantageous strategy. Science, 275, 1293–1295.

Bechara, A., Tranel, D., Damasio, H., Adolphs, R., Rockland, C., & Damasio, A. R. (1995). Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. Science, 269, 1115–1118.

Beck, A., Wüstenberg, T., Gensuck, A., Wrase, J., Schiagenhauf, F., Smolka, M. N., et al. (2012). Effect of brain structure, brain function, and brain connectivity on relapse in alcohol-dependent patients. Archives of General Psychiatry, 69, 842–852.

Beck, M., & Galef, B. G. (1989). Social influences on the selection of a protein-sufficient diet by Norway rats (*Rattus norvegicus*). Journal of Comparative Psychology, 103, 132–139.

Becker, A. E., Burwell, R. A., Gilman, S. E., Herzog, D. B., & Hamburg, P. (2002). Eating behaviours and attitudes following prolonged exposure to television among ethnic Fijian adolescent girls. British Journal of Psychiatry, 180, 509–514.

Bedny, M., Konkle, T., Pelphrey, K., Saxe, R., & Pascual-Leone, A. (2010). Sensitive period for a multimodal response in human visual motion area MT/MST. Current Biology, 20, 1900–1906.

Beecher, D. K. (1956). Relationship of significance of wound to pain experienced. Journal of the American Medical Association, 161, 1609–1613.

Begley, S., & Biddle, N. A. (1996, February 26). For the obsesssed, the mind can fix the brain. Newsweek, p. 60.

Begré, S., & Koenig, T. (2008). Cerebral disconnectivity: An early event in schizophrenia. Neuroscientist, 14, 19–45.

Behrmann, M., Moscovitch, M., & Winocur, G. (1994). Intact visual imagery and impaired visual perception in a patient with visual agnosia. Journal of Experimental Psychology: Human Perception and Performance, 20, 1068–1087.

Beisteiner, R., Matt, E., Fan, C., Baldysiak, H., Schönfeld, M., Novak, T. P., et al. (2020). Focal brain therapy: Transcranial pulse stimulation with ultrasound in Alzheimer's disease—A new navigated focal brain therapy. Advanced Science, 7(3). Retrieved from https://doi.org/10.1002/advs.202070017

Bekar, L., Libionka, W., Tian, G. F., Xu, Q., Torres, A., Wang, X., et al. (2008). Adenosine is crucial for deep brain stimulation-mediated attenuation of tremor. Nature Medicine, 14, 75–80.

Békésy, G. von. (1951). The mechanical properties of the ear. In S. S. Stevens (Ed.), The handbook of experimental psychology (pp. 1075–1115). New York, NY: Wiley.

Békésy, G. von. (1956). Current status of theories of hearing. Science, 123, 779–783.

Belfort, M. B., Anderson, P. J., Nowak, V. A., Lee, K. J., Molesworth, C., Thompson, D. K., et al. (2016). Breast milk feeding, brain development, and neurocognitive outcomes: A 7-year longitudinal study in infants born at less than 30 weeks' gestation. Journal of Pediatrics, 177, 133–139. doi:10.1016/j.jpeds.2016.06.045

Bell, A. P., Weinberg, M. S., & Hammersmith, S. K. (1981). Sexual preference. Bloomington: Indiana University Press.

Bellis, D. J. (1981). Heroin and politicians: The failure of public policy to control addiction in America. Westport, CT: Greenwood Press.

Benedict, C., Axelsson, T., Söderberg, S., Larsson, A., Ingelsson, E., Lind, L., & Schiöth, H. B. (2014). Fat mass and obesity-associated gene (FTO) is linked to higher plasma levels of the hunger hormone ghrelin and lower serum levels of the satiety hormone leptin in older adults. Diabetes, 63, 3955–3959.

Bennett, I. J., & Madden, D. J. (2014). Disconnected aging: Cerebral white matter integrity and age-related differences in cognition. Neuroscience, 276, 187–205.

Bennett, M. V. L., & Zukin, S. (2004). Electrical coupling and neuronal synchronization in the mammalian brain. Neuron, 41, 495–511.

Benoit, E., & Dubois, J. M. (1986). Toxin I from the snake *Dendroaspis polylepsis polylepsis*: A highly specific blocker of one type of potassium channel in myelinated nerve fiber. Brain Research, 377, 374–377.

Benros, M. E., Sörensen, H. J., Nielsen, P. R., Nordentoft, M., Mortensen, P. B., Petersen, L. (2015). The association between infections and general cognitive ability in young men—a nationwide study. PLoS One, 10(5), e0124005. Retrieved from

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0124005

Benson, D. F., Djenderedjian, A., Miller, B. L., Pachana, N. A., Chang, L., Itti, L., et al. (1996). Neural basis of confabulation. Neurology, 46, 1239–1243.

Benton, A. L. (1980). The neuropsychology of facial recognition. American Psychologist, 35(10), 176–186.

Bentz, E.-K., Hefler, L. A., Kaufmann, U., Huber, J. C., Kolbus, A., & Tempfer, C. B. (2008). A polymorphism of the *CYP17* gene related to sex steroid metabolism is associated with female-to-male but not male-to-female transsexualism. Fertility and Sterility, 90, 56–59.

Ben Zion, I. Z., Tessler, R., Cohen, L., Lerer, E., Raz, Y., Bachner-Melman, R., et al. (2006). Polymorphisms in the dopamine D4 receptor gene (*DRD4*) contribute to individual differences in human sexual behavior: Desire, arousal and sexual function. Molecular Psychiatry, 11, 782–786.

Berenbaum, S. A., Duck, S. C., & Bryk, K. (2000). Behavioral effects of prenatal *versus* postnatal androgen excess in children with 21-hydroxylase-deficient congenital adrenal hyperplasia. Journal of Clinical Endocrinology & Metabolism, 85, 727–733.

Berglund, A., Johannsen, T. H., Stockholm K., Viuff, M. H., Fedder, J., Main, K. M., et al. (2016). Incidence, prevalence, diagnostic delay, and clinical presentation of female 46,XY disorders of sex development. Journal of Clinical Endocrinology and Metabolism, 101, 4532–4540.

Berglund, H., Lindström, P., Dhejne-Helmy, C., & Savic, I. (2008). Male-to-female transsexuals show sex-atypical hypothalamus

activation when smelling odorous steroids. Cerebral Cortex, 18, 1900–1908.

Berhouma, M. (2013). Beyond the pineal gland assumption: A neuroanatomical appraisal of dualism in Descartes' philosophy. Clinical Neurology and Neurosurgery, 115(9), 1661–1670.

Berke, J., & Gould, S. (2019, March 26). New Jersey lawmakers postponed a critical vote to legalize marijuana—Here are all the states where pot is legal. Business Insider. Retrieved from https://www.businessinsider.com/legal-marijuana-states-2018-1

Berkman, N. D., Brownley, K. A., Peat, C. M., Lohr, K. N., Cullen, K. E., Morgan, L. C., et al. (2015). Management and outcomes of binge-eating disorder. Comparative Effectiveness Review No. 160. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from https://effectivehealthcare.ahrq.gov/products/binge-eating/research

Berlot, R., Metzler-Baddeley, C., Ikram, M. A., Jones, D. K., & O'Sullivan, M. J. (2016). Global efficiency of structural networks mediates cognitive control in mild cognitive impairment. Frontiers in Aging Neuroscience, 8, 292. Retrieved from https://www.frontiersin.org/articles/10.3389/fnagi.2016.00292/full

Berlucchi, G., & Aglioti, S. (1997). The body in the brain: Neural bases of corporeal awareness. Trends in Neurosciences, 20, 560–564.

Berman, M., Gladue, B., & Taylor, S. (1993). The effects of hormones, Type A behavior pattern, and provocation on aggression in men. Motivation and Emotion, 17, 125–138.

Bernaerts, S., Boets, B., Bosmans, G., Steyaert, J., & Alaerts, K. (2020). Behavioral effects of multiple-dose oxytocin treatment in

autism: a randomized, placebo-controlled trial with long-term follow-up. Molecular Autism, 11, 6. Retrieved from https://molecularautism.biomedcentral.com/articles/10.1186/s13229-020-0313-1

Bernstein, D. M., Laney, C., Morris, E. K., & Loftus, E. F. (2005). False beliefs about fattening foods can have healthy consequences. Proceedings of the National Academy of Sciences, 102, 13724–13731.

Bernstein, I. L. (1978). Learned taste aversions in children receiving chemotherapy. Science, 200, 1302–1303.

Bernstein, L. J., & Robertson, L. C. (1998). Illusory conjunctions of color and motion with shape following bilateral parietal lesions. Psychological Science, 9, 167–175.

Berridge, C. W., Devilbiss, D. M., Andrzejewski, M. E., Amsten, A. F., Kelley, A. E., Schmeichel, B., et al. (2006). Methyphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. Biological Psychiatry, 15, 1111–1120.

Bervoets, L., Van Hoorenbeeck, K., Kortleven, I., Van Noten, C., Hens, N., Vael, C., et al. (2013). Differences in gut microbiota composition between obese and lean children: A cross-sectional study. Gut Pathogens, 5, 10.

Besnard, P., Passilly-Degrace, P., & Khan, N. A. (2016). Taste of fat: A sixth taste modality? Physiology Review, 96, 151–176.

Bessa, J. M., Ferreira, D., Melo, I., Marques, F., Cerqueira, J. J., Palha, J. A., et al. (2009). The mood-improving actions of antidepressant do not depend on neurogenesis but are associated with neuronal remodeling. Molecular Psychiatry, 14, 764–773.

Bettinger, J. J., & Chu, R. (2020, February 5). Analgesics of the future: The potential of the endocannabinoid system. Practical Pain Management. Retrieved from https://www.practicalpainmanagement.com/treatments/pharmacological/analgesics-future-potential-endocannabinoid-system

Beveridge, T. J. R., Gill, K. E., Hanlon, C. A., & Porrino, L. J. (2008). Parallel studies of cocaine-related neural and cognitive impairment in humans and monkeys. Philosophical Transactions of the Royal Society B, 363, 3257–3266.

Bevilacqua, L., & Goldman, D. (2009). Genes and addictions. Clinical Pharmacologicy and Therapeutics, 85, 359–361.

Bhola, R., Kinsella, E., Giffin, N., Lipscombe, S., Ahmed, F., Weatherall, M., & Goadsby, P. J. (2015). Single-pulse transcranial magnetic stimulation (sTMS) for the acute treatment of migraine: Evaluation of outcome data for the UK post market pilot program. Journal of Headache and Pain. doi:10.1186/s10194-015-0535-3

Biederman, J. (2004). Impact of comorbidity in adults with attention-deficit/hyperactivity disorder. Journal of Clinical Psychiatry, 65, 3–7.

Biederman, J., & Faraone, S. V. (2005). Attention-deficit hyperactivity disorder. Lancet, 366, 237–248.

Biener, A., Cawley, J., & Meyerhoefer, C. (2017). The high and rising costs of obesity to the US health care system. Journal of General and Internal Medicine, 32(Suppl. 1), S6–S8.

Bienvenu, O. J., Samuels, J. F., Wuyek, L. A., Liang, K. Y., Wang, Y., Grados, M. A., et al. (2012). Is obsessive-compulsive disorder an anxiety disorder, and what, if any, are spectrum conditions? A family study perspective. Psychological Medicine, 42, 1–13.

Bienvenu, O. J., Wang, Y., Shugart, Y. Y., Welch, J. M., Grados, M. A., Fyer, A. J., et al. (2008). *Sapap3* and pathological grooming in humans: Results from the OCD collaborative genetics study. American Journal of Medical Genetics Part B, 150B, 710–720.

Billioud, G., Kruse, R. L., Carrillo, M., Whitten-Bauer, C., Gao, D., Kim, A., et al. (2016). In vivo reduction of hepatitis B virus antigenemia and viremia by antisense oligonucleotides. Journal of Hepatology, 64, 781–789.

Binder, E. B., Bradley, R. G., Liu, W., Epstein, M. P., Deveau, T. C., Mercer, K. B., et al. (2008). Association of *FKBP5* polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. Journal of the American Medical Association, 299, 1291–1305.

Binet, S., & Simon, T. (1905). Méthodes nouvelles pour le diagnostic du niveau intellectuel des anormaux [New methods for the diagnosis of the intellectual level of subnormals]. L'Année Psychologique, 12, 191–244.

Birbaumer, N., Lutzenberger, W., Montoya, P., Larbig, W., Unerti, K., Töpfner, S., et al. (1997). Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization. Journal of Neuroscience, 17, 5503–5508.

Birney, R. C., & Teevan, R. C. (1961). Instinct: An enduring problem in psychology. Princeton, NJ: Van Nostrand.

Bittar, R. G., Kar-Purkayastha, I., Owen, S. L., Bear, R. E., Green, A., Wang, S. Y., et al. (2005). Deep brain stimulation for pain relief: A meta-analysis. Journal of Clinical Neuroscience, 12, 515–519.

Bitterman, Y., Mukamel, R., Malach, R., Fried, I., & Nelken, I. (2008). Ultra-fine frequency tuning revealed in single neurons of human auditory cortex. Nature, 451, 197–202.

Black, M. H., Sacks, D. A., Xiang, A. H., & Lawrence, J. M. (2013). The relative contribution of prepregnancy overweight and obesity, gestational weight gain, and IADPSG-defined gestational diabetes mellitus to fetal overgrowth. Diabetes Care, 36, 56–62.

Black, N., & Robertson, M. (2010, August 19). Midnight snack? Not quite. ABC News/Health. Retrieved from http://abcnews.com/Health/MedicalMysteries/story?id=5483978

Blahak, C., Bazner, H., Capelle, H.-H., Wohrle, J., Weigel, R., Hennerici, M. G., et al. (2009). Rapid response of parkinsonian tremor to STN-DBS changes: Direct modulation of oscillatory basal ganglia activity? Movement Disorders, 24(8), 1221–1225.

Blake, M. (2014, June 19). Budget busting U.S. obesity costs climb past $300 billion a year. Fiscal Times. Retrieved from http://www.thefiscaltimes.com/Articles/2014/06/19/Budget-Busting-US-Obesity-Costs-Climb-Past-300-Billion-Year

Blanchard, D. C., & Blanchard, R. J. (1972). Innate and conditioned reactions to threat in rats with amygdaloid lesions. Journal of Comparative and Physiological Psychology, 81, 281–290.

Blanchard, R. (2018). Fraternal birth order, family size, and male homosexuality: Meta-analysis of studies spanning 25 years. Archives of Sexual Behavior, 47, 1–15.

Blanke, O., & Arzy, S. (2005). The out-of-body experience: Disturbed self-processing at the temporo-parietal junction. Neuroscientist, 11, 16–24.

Blehar, M. C., & Rosenthal, N. E. (1989). Seasonal affective disorders and phototherapy. Archives of General Psychiatry, 46, 469–474.

Blihar, D., Delgado, E., Buryak, M., Gonzalez, M., & Waechter, R. (2020). A systematic review of the neuroanatomy of dissociative identity disorder. Journal of Trauma & Dissociation (In press). Retrieved from https://www.sciencedirect.com/science/article/pii/S246874992030017X

Blinder, B. J., Cumella, E. J., & Sanathara, V. A. (2006). Psychiatric comorbidities of female inpatients with eating disorders. Psychosomatic Medicine, 68, 454–462.

Bloch, G. J., Butler, P. C., & Kohlert, J. G. (1996). Galanin microinjected into the medial preoptic nucleus facilitates female- and male-typical sexual behaviors in the female rat. Physiology and Behavior, 59, 1147–1154.

Bloch, G. J., Butler, P. C., Kohlert, J. G., & Bloch, D. A. (1993). Microinjection of galanin into the medial preoptic nucleus facilitates copulatory behavior in the male rat. Physiology and Behavior, 54, 615–624.

Bloom, J. S., Garcia-Barrera, M. A., Miller, C. J., Miller, S. R., & Hynd, G. W. (2013). Planum temporale morphology in children with developmental dyslexia. Neuropsychologia, 51, 1684–1692.

Bloomfield, M. A. P., Ashok, A. H., Volkow, N. D., & Howes, O. D. (2016). The effects of Δ9-tetrahydrocannabinol on the dopamine system. Nature, 539, 369–377.

Blum, D. (1994). The monkey wars. New York, NY: Oxford.

Blum, K., Madigan, M. A., Fried, L., Braverman, E. R., Giordano, J., & Badgaiyan, R. (2017). Coupling genetic addiction risk score (GARS) and pro dopamine regulation (KB220) to combat substance use disorder. Addiction & Rehabilitation Medicine, 11(2). doi:10.19080/GJARM.2017.01.555556

Bocklandt, S., Horvath, S., Vilain, E., & Hamer, D. H. (2006). Extreme skewing of X chromosome inactivation in mothers of homosexual men. Human Genetics, 118, 691–694.

Boecker, H., Dagher, A., Ceballos-Baumann, A. O., Passingham, R. E., Samuel, M., Friston, K. J., et al. (1998). Role of the human rostral supplementary motor area and the basal ganglia in motor sequence control: Investigations with H2 150 PET. Journal of Neurophysiology, 79, 1070–1080.

Bogaert, A. F. (2004). Asexuality: Prevalence and associated factors in a national probability sample. Journal of Sex Research, 41, 279–287.

Bogaert, A. F., Skorska, M. N., Wang, C., Gabrie, J., MacNeil, A. J., Hoffarth, M. R., et al. (2018). Male homosexuality and maternal immune responsivity to the Y-linked protein NLGN4Y. Proceedings of the National Academy of Sciences, 115, 302–306.

Bogardus, C., Lillioja, S., Ravussin, E., Abbott, W., Zawadzki, J. K., Young, A., et al. (1986). Familial dependence of the resting metabolic rate. New England Journal of Medicine, 315, 96–100.

Bohman, M. (1978). Some genetic aspects of alcoholism and criminality: A population of adoptees. Archives of General Psychiatry, 35, 269–276.

Boillat, M., Hammoudi, P.-M., Dogga, S. K., Pagès, S., Goubran, M., Rodriguez, I., & Soldati-Favre, D. (2019). Neuroinflammation-associated aspecific manipulation of mouse predator fear by Toxoplasma gondii. Cell Reports, 30, 320–334.

Boivin, D. B., Duffy, J. F., Kronauer, R. E., & Czeisler, C. A. (1996). Dose-response relationships for resetting of human circadian clock by light. Nature, 379, 540–542.

Boldog, E., Bakken, T. E., Hodge, R. D., Novotny, M., Aevermann, B. D. et al. (2018). Transcriptomic and morphophysiological evidence for a specialized human cortical GABAergic cell type. Nature Neuroscience, 21, 1185–1195.

Bolhuis, J. J., Okanoya, K., & Scharff, C. (2010). Twitter evolution: Converging mechanisms in birdsong and human speech. Nature Reviews: Neuroscience, 11, 747–759.

Bolles, R. C. (1975). Theory of motivation. New York, NY: Harper & Row.

Bonda, E., Petrides, M., Frey, S., & Evans, A. (1995). Neural correlates of mental transformations of the body-in-space. Proceedings of the National Academy of Sciences, 92, 11180–11184.

Bonebakker, A. E., Bonke, B., Klein, J., Wolters, G., Stijnene, T., Passchier, J., et al. (1996). Information processing during general anesthesia: Evidence for unconscious memory. Memory and Cognition, 24, 766–776.

Bontempi, B., Laurent-Demir, C., Destrade, C., & Jaffard, R. (1999). Time-dependent reorganization of brain circuitry underlying long-term memory storage. Nature, 400, 671–675.

Bor, D. (2013). This is your brain on consciousness. New Scientist, 218, 32–34.

Bor, D., & Seth, A. K. (2012). Consciousness and the prefrontal parietal network: Insights from attention, working memory, and chunking. Frontiers in Psychology, 3, Article 63. Retrieved from http://journal.frontiersin.org/Journal/10.3389/fpsyg.2012.00063/abstract

Boring, E. G. (1942). Sensation and perception in the history of psychology. New York, NY: Appleton-Century.

Born, R. T., & Bradley, D. C. (2005). Structure and function of visual area MT. Annual Review of Neuroscience, 28, 157–189.

Borsook, D., Becerra, L., Fishman, S., Edwards, A., Jennings, C. L., Stojanovic, M., et al. (1998). Acute plasticity in the human somatosensory cortex following amputation. Neuroreport, 9, 1013–1017.

Bortsov, A. V., Platts-Mills, T. F., Peak, D. A., Jones, J. S., Swor, R. A., Domeier, R. M., et al. (2013). Pain distribution and predictors of widespread pain in the immediate aftermath of motor vehicle collision. European Journal of Pain, 17(8), 1243–1251.

Bortsov, A. V., Smith, J. E., Diatchenko, L., Soward, A. C., Ulirsch, J. C., Rossi, C., et al. (2013). Polymorphisms in the clucocorticoid receptor co-chaperone FKBP5 predict persistent musculoskeletal pain after traumatic stress exposure. Pain, 154, 1419–1426.

Bottini, G., Corcoran, R., Sterzi, R., Paulesu, E., Schenone, P., Scarpa, P., et al. (1994). The role of the right hemisphere in the interpretation of figurative aspects of language: A positron emission tomography activation study. Brain, 117, 1241–1253.

Bouchard, C. (1989). Genetic factors in obesity. Medical Clinics of North America, 73, 67–81.

Bouchard, C., Tremblay, A., Després, J.-P., Nadeau, A., Lupien, P. J., Thériault, G., et al. (1990). The response to long-term overfeeding in identical twins. New England Journal of Medicine, 322, 1477–1482.

Bouchard, M. F., Bellinger, D. C., Wright, R. O., & Weisskopf, M. G. (2010). Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. Pediatrics, 125, e1270–e1277.

Bouchard, M. F., Chevrier, J., Harley, K. G., Kogut, K., Vedar, M., Calderon, N., et al. (2011). Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. Environmental Health Perspectives, 119, 1189–1195.

Bouchard, T. J. (1994). Genes, environment, and personality. Science, 264, 1700–1701.

Bouchard, T. J., Jr., & McGue, M. (1981). Familial studies of intelligence: A review. Science, 212, 1055–1059.

Bouchard, T. J., & Segal, N. L. (1985). Environment and IQ. In B. B. Wolman (Ed.), Handbook of intelligence: Theories, measurements, and applications (pp. 391–464). New York, NY: Wiley.

Bouhali, F., de Schotten, M. T., Pinel, P., Poupon, C., Mangin, J.-F., Dehaene, S., & Cohen, L. (2014). Anatomical connections of the visual word form area. Journal of Neuroscience, 34, 15402–15414.

Boulenguez, P., & Vinay, L. (2009). Strategies to restore motor functions after spinal cord injury. Current Opinion in Neurobiology, 19, 587–600.

Bourgeois, J.-P., & Rakic, P. (1993). Changes of synaptic density in the primary visual cortex of the macaque monkey from fetal to adult stage. Journal of Neuroscience, 13, 2801–2820.

Bouvier, S. E., & Engel, S. A. (2006). Behavioral deficits and cortical damage loci in cerebral achromatopsia. Cerebral Cortex, 16, 183–191.

Bowmaker, J. K., & Dartnall, H. J. A. (1980). Visual pigments of rods and cones in a human retina. Journal of Physiology (London), 298, 501–511.

Bozarth, M. A., & Wise, R. A. (1985). Toxicity associated with long-term intravenous heroin and cocaine self-administration in the rat. Journal of the American Medical Association, 254, 81–83.

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. Acta Neuropathology, 82, 239–259.

Braak, H., Del Tredici, K., Rüb, U., de Vos, R. A. I., Steur, E. N. H. J., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. Neurobiology, 24, 197–211.

Bracha, H. S., Torrey, E. F., Gottesman, I. I., Bigelow, L. B., & Cunniff, C. (1992). Second-trimester markers of fetal size in schizophrenia: A study of monozygotic twins. American Journal of Psychiatry, 149, 1355–1361.

Bradbury, J. (2003). Why do men and women feel and react to pain differently? Lancet, 361, 2052–2053.

Bradbury, T. N., & Miller, G. A. (1985). Season of birth in schizophrenia: A review of evidence, methodology, and etiology. Psychological Bulletin, 98, 569–594.

Branch, J. (2015, July 27). Dutee Chand, female sprinter with high testosterone level, wins right to compete. New York Times. Retrieved from https://www.nytimes.com/2015/07/28/sports/international/dutee-chand-female-sprinter-with-high-male-hormone-level-wins-right-to-compete.html?_r=0

Brang, D., & Ramachandran, V. S. (2011). Survival of the synesthesia gene: Why do people hear colors and taste words? PLoS Biology, 9, e1001205. Retrieved from http://www.plosbiology.org/article/info:doi/10.1371/journal.pbio.1001205

Brannon, E. M., & Terrace, H. S. (1998). Ordering of the numerosities 1 to 9 by monkeys. Science, 282, 746–749.

Bratsberg, B., & Rogeberg, O. (2018). Flynn effect and its reversal are both environmentally caused. Proceedings of the National Academy of Sciences, 115, 6674–6678.

Braun, B. G. (1985). Treatment of multiple personality disorder. Washington, DC: American Psychiatric Press.

Braun, M., Wendt, A., Karanauskaite, J., Galvanovskis, J., Clark, A., MacDonald, P. E., & Rorsman, P. (2007). Corelease and differential exit via the fusion pore of GABA, serotonin, and ATP from LDCV in rat pancreatic β cells. Journal of General Physiology, 129, 221–231.

Bray, G. A. (1992). Drug treatment of obesity. American Journal of Clinical Nutrition, 55, 538S–544S.

Breasted, J. H. (1930). The Edwin Smith surgical papyrus. Chicago, IL: University of Chicago Press.

Brecher, E. M. (1972). Licit and illicit drugs. Boston, MA: Little, Brown.

Breen, G., Webb, B. T., Butler, A. W., van den Oord, E. J. C. G., Tozzi, F., Craddock, N., et al. (2011). A genome-wide significant linkage for severe depression on chromosome 3: The depression network study. American Journal of Psychiatry, 168, 840–847.

Breitner, J. C., Folstein, M. E., & Murphy, E. A. (1986). Familial aggregation in Alzheimer dementia-1: A model for the age-dependent expression of an autosomal dominant gene. Journal of Psychiatric Research, 20, 31–43.

Bremer, J. (1959). Asexualization: A follow-up study of 244 cases. New York, NY: Macmillan.

Brent, D. A., & Melhem, N. (2008). Familial transmission of suicidal behavior. Psychiaritc Clinics of North America, 31, 157–177.

Breslow, J. M. (2015a). New: 87 deceased NFL players test positive for brain disease. Frontline. Retrieved from http://www.pbs.org/wgbh/frontline/article/new-87-deceased-nfl-players-test-positive-for-brain-disease

Breslow, J. M. (2015b). NFL concussion settlement wins final approval from judge. Frontline. Retrieved from http://www.pbs.org/wgbh/frontline/article/nfl-concussion-settlement-wins-final-approval-from-judge

Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. E. (1998). Making memories: Brain activity that predicts how well visual experience will be remembered. Science, 281, 1185–1187.

Brickman, A. M., Khan, U. A., Provenzano, F. A., Yeung, L.-K., Suzuki, W., Schroeter, H., et al. (2014). Enhancing dentate gyrus function with dietary flavanols improves cognition in older adults. Nature Neuroscience, 17, 1798–1803.

A brighter day for Edward Taub. (1997). Science, 276, 1503.

Brikell, I., Kuja-Halkola, R., & Larsson, H. (2015). Heritability of attention-deficit hyperactivity disorder in adults. American Journal

of Medical Genetics, B, 168B, 406–413.

Briley, D. A., & Tucker-Drob, E. M. (2013). Explaining the increasing heritability of cognitive ability across development: a meta-analysis of longitudinal twin and adoption studies. Psychological Science, 24, 1704–1713.

Brinkman, C. (1984). Supplementary motor area of the monkey's cerebral cortex: Short- and long-term deficits after unilateral ablation and the effects of subsequent callosal section. Journal of Neuroscience, 4, 918–929.

Britten, K. H. (2008). Mechanisms of self-motion perception. Annual Review of Neuroscience, 31, 389–410.

Britten, R. J. (2002). Divergence between samples of chimpanzee and human DNA sequences is 5%, counting indels. Proceedings of the National Academy of Sciences, 99, 13633–13635.

Broberger, C., & Hökfelt, T. (2001). Hypothalamic and vagal neuropeptide circuitries regulating food intake. Physiology and Behavior, 74, 669–682.

Broca, P. (1861). Remarques sur le siège de la faculté du langage articulé, suivies d'une observation d'aphemie (perte de la parole). Bulletin de la Société Anatomique (Paris), 36, 330–357.

Broughton, R. (1975). Biorhythmic variations in consciousness and psychological functions. Canadian Psychological Review, 16, 217–239.

Broughton, R., Billings, R., Cartwright, R., Doucette, D., Edmeads, J., Edward, H. M., et al. (1994). Homicidal somnambulism: A case report. Sleep, 17, 253–264.

Brower, L. B. (1969). Ecological chemistry. Scientific American, 220(2), 22–29.

Brown, A. S., Begg, M. D., Gravenstein, S., Schaefer, C. A., Wyatt, R. J., Bresnahan, M., et al. (2004). Serologic evidence of prenatal influenza in the etiology of schizophrenia. Archives of General Psychiatry, 61, 774–780.

Brown, K., & Wald, G. (1964). Visual pigments in single rods and cones of the human retina. Science, 143, 45–52.

Brown, M. T., Murphy, F. T., Radin, D. M., Davignon, I., Smith, M. D., & West, C. R. (2013). Tanezumab reduces osteoarthritic hip pain. Arthritis & Rheumatism, 65(7), 1795–1803.

Brown, R. H., Cannon, S. C., & Rowland, L. P. (2013). Diseases of the nerve and motor unit. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), Principles of neural science (5th ed., pp. 307–336). New York, NY: McGraw-Hill.

Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. S. (2009). Default-mode brain dysfunction in mental disorders: A systematic review. Neuroscience and Biobehavioral Reviews, 33, 279–296.

Bryson, S. (2020, March 19). Gene therapy reprograms brain cells in mouse model, improves motor function. Huntington's Disease News. Retrieved from https://huntingtonsdiseasenews.com/2020/03/19/gene-therapy-reprograms-damaged-brain-cells-functioning-neurons-huntingtons-mouse-model

Bucci, M. P., Bremond-Gignac, D., & Kapoula, Z. (2008). Latency of saccades and vergence eye movements in dyslexic children. Experimental Brain Research, 188(1), 1–12. doi:10.1007/s00221-008-1345-5

Buchanan, T. W., Lutz, K., Mirzazade, S., Specht, K., Shah, N. J., Zilles, K., et al. (2000). Recognition of emotional prosody and verbal components of spoken language: An fMRI study. Cognitive Brain Research, 9, 227–238.

Buchwald, H., Avidor, Y., Braunwald, E., Jensen, M. D., Pories, W., Fahrbach, K., et al. (2004). Bariatric surgery: A systematic review and meta-analysis. Journal of the American Medical Association, 292, 1724–1737.

Buchwald, H., Estok, R., Fahrbach, K., Banel, D., Jensen, M. D., Pories, W. J., et al. (2009). Weight and type 2 diabetes after bariatric surgery: Systematic review and meta-analysis. American Journal of Medicine, 122, 248–256.

Buckley, N. A., Dawson, A. H., & Isbister, G. K. (2014). Serotonin syndrome. British Medical Journal, 348, 33–35.

Buckner, R. L., & Koutstaal, W. (1998). Functional neuroimaging studies of encoding, priming, and explicit memory retrieval. Proceedings of the National Academy of Sciences, 95, 891–898.

Buell, S. J., & Coleman, P. D. (1979). Dendritic growth in the aged human brain and failure of growth in senile dementia. Science, 206, 854–856.

Bulik, C. M., Sullivan, P. F., Tozzi, F., Furberg, H., Lichtenstein, P., & Pedersen, N. L. (2006). Prevalence, heritability and prospective risk factors for anorexia nervosa. Archives of General Psychiatry, 63, 305–312.

Bulik, C. M., Sullivan, P. F., Wade, T. D., & Kendler, K. S. (2000). Twin studies of eating disorders: A review. International Journal of Eating Disorders, 27, 1–20.

Bunney, B. G., Li, J. Z., Walsh, D. M., Stein, R., Vawter, M. P., Cartagena, P., et al. (2015). Circadian dysregulation of clock genes: Clues to rapid treatments in major depressive disorder. Molecular Psychiatry, 20, 48–55.

Bunney, W. E., Jr., Murphy, D. L., Goodwin, F. K., & Borge, G. F. (1972). The “switch process” in manic-depressive illness: I. A systematic study of sequential behavioral changes. Archives of General Psychiatry, 27, 295–302.

Buñuel, L. (1983). My last sigh. New York, NY: Knopf.

Burgess, A., Dubey, S., Yeung, S., Hough, O., Eterman, N., Aubert, I., & Hynynen, K. (2014). Alzheimer disease in a mouse model: MR imaging-guided focused ultrasound targeted to the hippocampus opens the blood-brain barrier and improves pathologic abnormalities and behavior. Radiology, 273, 736–745.

Burke, S. M., Cohen-Kettenis, P. T., Veltman, D. J., Klink, D. T., & Bakker, J. (2014). Hypothalamic response to the chemo-signal androstadienone in gender dysphoric children and adolescents. Frontiers in Endocrinology, 5(60), 1–10.

Burke, S. N., & Barnes, C. A. (2006). Neural plasticity in the ageing brain. Nature Reviews Neuroscience, 7, 30–40.

Burkett, J. P., Andari, E., Johnson, Z. V., Curry, D. C., de Waal, F. B. M., & Young, L. J. (2016). Oxytocin-dependent consolation behavior in rodents. Science, 351, 375–378.

Buschman, T. J., & Miller, E. K. (2007). Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science, 315, 1860–1862.

Bushdid, C., Magnasco, M. O., Vosshall, L. B., & Keller, A. (2014). Humans can discriminate more than 1 trillion olfactory stimuli. Science, 343, 1370–1372.

Bushnell, I. W. (2001). Mother's face recognition in newborn infants: Learning and memory. Infant and Child Development, 10, 67–74.

Butterworth, B. (1999). A head for figures. Science, 284, 928–929.

Buxhoeveden, D. P., & Casanova, M. F. (2002). The minicolumn hypothesis in neuroscience. Brain, 125, 935–951.

Buysse, D. J., Angst, J., Gamma, A., Ajdacic, V., Eich, D., & Rössler, W. (2008). Prevalence, course, and comorbidity of insomnia and depression in young adults. Sleep, 31, 473–480.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: Compensatory brain activity in high-performing older adults. NeuroImage, 17, 1394–1402.

Caffeine prevents post-op headaches. (1996). United Press International, MSNBC. Retrieved from https://www.msnbc.com/news/36911.asp

Caggiula, A. R. (1970). Analysis of the copulation-reward properties of posterior hypothalamic stimulation in male rats. Journal of Comparative and Physiological Psychology, 70, 399–412.

Cahill, L. (2006). Why sex matters for neuroscience. Nature Reviews Neuroscience, 7, 477–484.

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., et al. (1996). Amygdala activity at encoding correlated with long-term,

free recall of emotional information. Proceedings of the National Academy of Sciences, 93, 8016–8021.

Calem, M., Bromis, K., McGuire, P., Morgan, C., & Kempton, M. J. (2017). Meta-analysis of associations between childhood adversity and hippocampus and amygdala volume in non-clinical and general population samples. Neuroimage: Clinical, 14, 471–479.

Calles-Escandón, J., & Horton, E. S. (1992). The thermogenic role of exercise in the treatment of morbid obesity: A critical evaluation. American Journal of Clinical Nutrition, 55, 533S–537S.

Calvo, N., Abrevaya, S., Martinez-Cuitino, M., Steeb, B., Zamora, D., Sedeno, L., et al. (2019). Rethinking the neural basis of prosody and non-literal language: Spared pragmatics and cognitive compensation in a bilingual with extensive right-hemisphere damage. Frontiers in Psychology, 10, A570.

Campbell, C. M., & Edwards, R. R. (2012). Ethnic differences in pain and pain management. Pain Management, 2, 219–230.

Campbell, S. S., & Tobler, I. (1984). Animal sleep: A review of sleep duration across phylogeny. Neuroscience and Biobehavioral Reviews, 8, 269–300.

Camperio Ciani, A., Cermelli, P., & Zanzotto, G. (2008). Sexually antagonistic selection in human male homosexuality. PLoS ONE, 3, e2282. Retrieved from https://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0002282

Camperio Ciani, A., Corna, F., & Capiluppi, C. (2004). Evidence for maternally inherited factors favouring male homosexuality and promoting female fecundity. Proceedings of the Royal Society of London B, 271, 2217–2221.

Canavan, A. G. M., Sprengelmeyer, R., Diener, H.-C., & Hömberg, V. (1994). Conditional associative learning is impaired in cerebellar disease in humans. Behavioral Neuroscience, 108, 475–485.

Cannon, M., Jones, P. B., & Murray, R. M. (2002). Obstetric complications and schizophrenia: Historical and meta-analytic review. American Journal of Psychiatry, 159, 1080–1092.

Cannon, W. B. (1942). “Voodoo” death. American Anthropologist, 44, 169–181.

Cantalupo, C., Oliver, J., Smith, J., Nir, T., Taglialatela, J. P., & Hopkins, W. D. (2009). The chimpanzee brain shows human-like perisylvian asymmetries in white matter. European Journal of Neuroscience, 30, 431–438.

Cao, Y. Q., Mantyh, P. W., Carlson, E. J., Gillespie, A. M., Epstein, C. J., & Basbaum, A. I. (1998). Primary afferent tachykinins are required to experience moderate-to-intense pain. Nature, 392, 390–394.

Cao-Lei, L., Massart, R., Suderman, M. J., Macnes, Z., Elgbeili, G., Laplante, D. P., & Szyf, M. (2014). DNA methylation signatures triggered by prenatal maternal stress exposure to a natural disaster: Project Ice Storm. PLoS ONE, 9(9), e107653. Retrieved from https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0107653

Cardno, A. G., & Gottesman, I. I. (2000). Twin studies of schizophrenia: From bow-and-arrow concordances to *Star Wars* Mx and functional genomics. American Journal of Medical Genetics, 97, 12–17.

Cariani, P. A. (2004). Temporal codes and computations for sensory representation and scene analysis. IEEE Transactions on Neural Networks, 15, 1100–1111.

Carlson, M. (1981). Characteristics of sensory deficits following lesions of Brodmann's areas 1 and 2 in the postcentral gyrus of Macaca mulatta. Brain Research, 204, 424–430.

Carlsson, H.-E., Hagelin, J., & Hau, J. (2004). Implementation of the Three Rs in biomedical research. Veterinary Record, 154, 467–470.

Carmichael, M. S., Warburton, V. L., Dixen, J., & Davidson, J. D. (1994). Relationships among cardiovascular, muscular, and oxytocin responses during human sexual activity. Archives of Sexual Behavior, 23, 59–79.

Carr, C. E., & Konishi, M. (1990). A circuit for detection of interaural time differences in the brain stem of the barn owl. Journal of Neuroscience, 10, 3227–3246.

Carr, K. W., White-Schwoch, T., Tierney, A. T., Strait, D. L., & Kraus, N. (2014). Beat synchronization predicts neural speech encoding and reading readiness in preschoolers. Proceedings of the National Academy of Sciences, 111(40), 14559–14564.

Carraher, T. N., Carraher, D. W., & Schliemman, A. D. (1985). Mathematics in the streets and in schools. British Journal of Developmental Psychology, 3, 21–29.

Carrera, M. R., Ashley, J. A., Parsons, L. H., Wirsching, P., Koob, G. F., & Janda, K. D. (1995). Suppresssion of psychoactive effects of cocaine by active immunization. Nature, 378, 727–730.

Carroll, J. B. (1993). Human cognitive abilities: A survey of factor-analytic studies. Cambridge, UK: University of Cambridge Press.

Cascio, C. J., Foss-Feig, J. H., Burnette, C. P., Heacock, J. L., & Cosby, A. A. (2012). The rubber hand illusion in children with

autism spectrum disorders: Delayed influence of combined tactile and visual input on proprioception. Autism, 16, 406–419.

Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., et al. (2002). Role of genotype in the cycle of violence in maltreated children. Science, 297, 851–854.

Cassin, S., & von Ranson, K. (2005). Personality and eating disorders: A decade in review. Clinical Psychology Review, 25, 895–916.

Castellano-Castillo, D., Moreno-Indias, I., Sanchez-Alcoholado, L., Ramos-Molina, B., Alcalde-Torres, J., Morcillo, S., et al. (2019). Altered adipose tissue DNA methylation status in metabolic syndrome: Relationships between global DNA methylation and specific methylation at adipogenic, lipid metabolism and inflammatory candidate genes and metabolic variables. Journal of Clinical Medicine, 8, E87. doi:10.3390/jcm8010087

Castellanos, F. X., & Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: The search for endophenotypes. Nature Reviews Neuroscience, 3, 617–628.

Castles, A., & Friedmann, N. (2014). Developmental dyslexia and the phonological deficit hypothesis. Mind & Language, 29, 270–285.

Cattaneo, A. (2010). Tanezumab, a recombinant humanized mAb against nerve growth factor for the treatment of acute and chronic pain. Current Opinion in Molecular Therapeutics, 12, 94–105.

Catterall, W. A. (1984). The molecular basis of neuronal excitability. Science, 223, 653–661.

Catterall, W. A. (2010). Ion channel voltage sensors: Structure, function, and pathophysiology. Neuron, 67, 915–928.

Caunca, M. R., Gardener, H., Simonetto, M., Cheung, Y. K., Alperin, N., Yoshgita, M., et al. (2019). Measures of obesity are associated with MRI markers of brain aging. Neurology, 93, e791-e803. doi:10.1212/WNL.0000000000007966

Caye, A., Rocha, T. B.-M., Anselmi, L., Murray, J., Menezes, A. M. B., Barros, F. D., et al. (2016). Attention-deficit/hyperactivity disorder trajectories from childhood to young adulthood: Evidence from a birth cohort supporting a late-onset syndrome. JAMA Psychiatry, 73, 705–712.

Ceci, S. J., & Liker, J. (1986). A day at the races: A study of IQ, expertise, and cognitive complexity. Journal of Experimental Psychology: General, 115, 255–266.

Centers for Disease Control and Prevention. (2015a). Leading causes of death. Retrieved from http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm

Centers for Disease Control and Prevention. (2015b). Smoking & tobacco use. Retrieved from http://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/

Centers for Disease Control and Prevention. (2017, March 17). Traumatic brain injury-related emergency department visits, hospitalizations, and deaths—United States, 2007 and 2013. Surveillance Summaries, 66, 1–16.

Centers for Disease Control and Prevention. (2018). Understanding the epidemic. Retrieved from https://www.cdc.gov/drugoverdose/epidemic/index.html

Centers for Disease Control and Prevention. (2019). Measles cases and outbreaks. Retrieved from https://www.cdc.gov/measles/cases-outbreaks.html

Centers for Disease Control and Prevention. (2020a). Data & statistics on autism spectrum disorder. Retrieved from https://www.cdc.gov/ncbddd/autism/data.html

Centers for Disease Control and Preventions. (2020b). Prevalence of autism spectrum disorder among children aged 8 years—Autism and developmental disabilities monitoring network, 11 sites, United States, 2016. Morbidity and Mortality Weekly Report (MMWR). Retrieved from https://www.cdc.gov/mmwr/volumes/69/ss/ss6904a1.htm?s_cid=ss6904a1_w

Chai, G., Governale, L., McMahon, A. W., Trinidad, J. P., Staffa, J., & Murphy, D. (2012). Trends of outpatient prescription drug utilization in US children, 2002–2010. Pediatrics, 130, 23–31.

Chakrabarti, B., Bullmore, E., & Baron-Cohen, S. (2006). Empathizing with basic emotions: Common and discrete neural substrates. Social Neuroscience, 1, 364–384.

Chalavi, S., Vissia, E. M., Giesen, M. E., Nijenhuis, E. R. S., Draijer, N., Barker, G. J., & Reinders, A. A. T. S. (2015). Similar cortical but not subcortical gray matter abnormalities in women with posttraumatic stress disorder with versus without dissociative identity disorder. Psychiatry Research Neuroimaging, 231, 308–319.

Chalavi, S., Vissia, E. M., Giesen, M. E., Nijenhuis, E. R. S., Draijer, N., Cole, J. H., et al. (2015). Abnormal hippocampal morphology in dissociative identity disorder and post-traumatic stress disorder correlates with childhood trauma and dissociative symptoms. Human Brain Mapping, 36, 1692–1704.

Chamberlain, S. R., Menzies, L., Hampshire, A., Suckling, J., Fineberg, N. A., de Campo, N., et al. (2008). Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. Science, 321, 421–422.

Chan, B. L., Witt, R., Charrow, A. P., Magee, A., Howard, R., & Pasquina, P. F. (2007). Mirror therapy for phantom limb pain. New England Journal of Medicine, 357, 2206–2207.

Chang, M. M., & Leeman, S. E. (1970). Isolation of a sialogogic peptide from bovine hypothalamic tissue and its characterization as substance P. Journal of Biological Chemistry, 245, 4784–4790.

Chapman, P. F., White, G. L., Jones, M. W., Cooper-Blacketer, D., Marshall, V. J., Irizarry, M., et al. (1999). Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. Nature Neuroscience, 2, 271–276.

Chatelle, C., Thibaut, A., Gosseries, O., Bruno, M.-A., Demertzi, A., Bernard, C., et al. (2014). Changes in cerebral metabolism in patients with a minimally conscious state responding to zolpidem. Frontiers in Human Neuroscience. doi:10.3389/fnhum.2014.00917

Chatterton, Z., Hartley, B. J., Seok, M.-H., Mendelev, N., Chen, S., Milekic, M., et al. (2017). In utero exposure to maternal smoking is associated with DNA methylation alterations and reduced neuronal content in the developing fetal brain. Epigenetics & Chromatin, 10, 4. doi:10.1186/s13072-017-0111-y

Chau, A., Salazar, A. M., Krueger, F., Cristofori, I., & Grafman, J. (2015). The effect of claustrum lesions on human consciousness and recovery of function. Consciousness and Cognition, 36, 256–264.

Chaudhari, N., Pereira, E., & Roper, S. D. (2009). Taste receptors for umami: The case for multiple receptors. American Journal of Clinical Nutrition, 90(Suppl.), 738S–742S.

Chawla, D., Rees, G., & Friston, K. J. (1999). The physiological basis of attentional modulation in extrastriate visual areas. Nature Neuroscience, 2, 671–675.

Check, E. (2004). Cardiologists take heart from stem-cell treatment success. Nature, 428, 880.

Chen, D. F., Schneider, G. E., Martinou, J.-C., & Tonegawa, S. (1997). Bcl-2 promotes regeneration of severed axons in mammalian CNS. Nature, 385, 434–438.

Chen, F., Liu, P., Gu, Y., Zhu, Z., Nanisetti, A., Lan, Z., et al. (2017). Isolation and whole genome sequencing of fetal cells from maternal blood towards the ultimate non-invasive prenatal testing. Prenatal Diagnosis, 37, 1311–1321.

Chen, F. S., Kumsta, R., von Dawans, B., Monakhov, M., Ebstein, R. P., & Heinrichs, M. (2011). Common oxytocin receptor gene (OXTR) polymorphisms and social support interact to reduce stress in humans. Proceedings of the National Academy of Sciences, 108, 19937–19942.

Chen, J.-F., Xu, K., Petzer, J. P., Staal, R., Xu, Y.-H., Beilstein, M., et al. (2001). Neuroprotection by caffeine and A2a adenosine receptor inactivation in a model of Parkinson's disease. Journal of Neuroscience, 21, 1–6.

Chen, L., Wassermann, D., Abrams, D. A., Kochalka, J., Gallardo-Diez, G., & Menon, V. (2019). The visual word form area (VWFA) is part of both language and attention circuitry. Nature Communications, 10, 5601. Retrieved from https://www.nature.com/articles/s41467-019-13634-z

Chen, M. C., Hamilton, J. P., & Gotlib, I. H. (2010). Decreased hippocampal volume in healthy girls at risk of depression. Archives of General Psychiatry, 67, 270–276.

Chen, X., Gabitto, M., Peng, Y., Ryba, N. J. P., & Zuker, C. S. (2011). A gustotopic map of taste qualities in the mammalian brain. Science, 333, 1262–1266.

Chen, Y.-C., Auer-Grumbach, M., Matsukawa, S., Zitzelsberger, M., Themistocleous, A. C., Strom, T. M., et al. (2015). Transcriptional regulator PRDM12 is essential for human pain perception. Nature Genetics, 47(7), 803–808.

Cherrier, M. M., Craft, S., & Matsumoto, A. H. (2003). Cognitive changes associated with supplementation of testosterone or dihydrotestosterone in mildly hypogonadal men: A preliminary report. Journal of Andrology, 24, 568–576.

Cherrier, M. M., Matsumoto, A. H., Amory, J. K., Ahmed, S., Bremner, W., Peskind, E. R., et al. (2005). The role of aromatization in testosterone supplementation. Neurology, 64, 290–296.

Cherry, J. A., & Baum, M. J. (2019). Sex differences in main olfactory ssytem pathways involved in psychosexual function. Genes, Brain and Behavior, e12618. Retrieved from https://doi.org/10.1111/gbb.12618

Chi, R. P., & Snyder, A. W. (2012). Brain stimulation enables the solution of an inherently difficult problem. Neuroscience Letters, 515, 121–124.

Chiang, M.-C., Barysheva, M., McMahon, K. L., de Zubicaray, G. I., Johnson, K., Montgomery, G. W., et al. (2012). Gene network effects on brain microstructure and intellectual performance identified in 472 twins. Journal of Neuroscience, 32, 8732–8745.

Chiang, M.-C., Barysheva, M., Shattuck, D. W., Lee, A. D., Madsen, S. K., Avedissian, C., et al. (2009). Genetics of brain fiber architecture and intellectual performance. Journal of Neuroscience, 29, 2212–2224.

Chivers, T. (2019, June 23). What do we do about fake video? The Guardian. Retrieved from

https://www.theguardian.com/technology/2019/jun/23/what-do-we-do-about-deepfake-video-ai-facebook

Cho, A. K. (1990). Ice: A new dosage form of an old drug. Science, 249, 631–634.

Choi, S. H., Kim, Y. H., Hebisch, M., Sliwinski, C., Lee, S., D'Avanzo, C., et al. (2014). A three-dimensional human neural cell culture model of Alzheimer's disease. Nature, 515, 274–278.

Chomsky, N. (1980). Rules and representations. New York, NY: Columbia University Press.

Chong, S. Y. C., Ptáček, L. J., & Fu, Y.-H. (2012). Genetic insights on sleep schedules: This time, it's *PER*sonal. Cell, 28, 598–605.

Choquet, H., & Meyre, D. (2011). Genetics of obesity: What have we learned? Current Genomics, 12, 169–179.

Chou, Y., Hickey, P. T., Sundman, M., Song, A. W., & Chen, N. (2015). Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson disease. JAMA Neurology, 72, 432–440.

Chowdhury, R., Guitart-Masip, M., Bunzeck, N., Dolan, R. J., & Düzel, E. (2012). Dopamine modulates episodic memory persistence in old age. Journal of Neuroscience, 32, 14193–14204.

Christison-Lagay, K. L., Gifford, A. M., & Cohen, Y. E. (2015). Neural correlates of auditory scene analysis and perception. International Journal of Psychophysiology, 95, 238–245.

Chuang, R. S.-I., Jaffe, H., Cribbs, L., Perez-Reyes, E., & Swartz, K. J. (1998). Inhibition of T-type voltage-gated calcium channels by a new scorpion toxin. Nature Neuroscience, 1, 668–674.

Chung, K., Wallace, J., Kim, S.-Y., Kalyanasundaram, S., Andalman, A. S., Davidson, T. J., et al. (2013). Structural and molecular interrogation of intact biological systems. Nature, 497, 332–337.

Church, T. S., Thomas, D. M., Tudor-Locke, C., Katzmarzyk, P. T., Earnest, C. P., Rodarte, R. Q., et al. (2011). Trends over 5 decades in U.S. occupation-related physical activity and their associations with obesity. PLoS ONE, 6, e19657.

Cicchetti, F., Seporta, S., Hauser, R. A., Parent, M., Saint-Pierre, M., Sanberg, P. R., et al. (2009). Neural transplants in patients with Huntington's disease undergo disease-like neuronal degeneration. Proceedings of the National Academy of Sciences, 106, 12483–12488.

Cima, M., Smeets, T., & Jelicic, M. (2008). Self-reported trauma, cortisol levels, and aggression in psychopathic and non-psychopathic prison inmates. Biological Psychology, 78, 75–86.

Ciompi, L. (1980). Catamnestic long-term study on the course of life and aging of schizophrenics. Schizophrenia Bulletin, 6, 607–618.

Cirelli, C., Gutierrez, C. M., & Tononi, G. (2004). Extensive and divergent effects of sleep and wakefulness on brain gene expression. Neuron, 41, 35–43.

Clarkson, A. N., Huang, B. S., MacIsaac, S. E., Mody, I., & Carmichael, T. (2010). Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. Nature, 468, 305–309.

Clarren, S. K., Alvord, E. C., Sumi, S. M., Streissguth, A. P., & Smith, D. W. (1978). Brain malformations related to prenatal exposure to alcohol. Journal of Pediatrics, 92, 64–67.

Cloninger, C. R. (1987). Neurogenetic adaptive mechanisms in alcoholism. Science, 236, 410–416.

Clopath, C. (2012). Synaptic consolidation: An approach to long-term learning. Cognitive Neurodynamics, 6, 251–257.

Cloutier, M., Aigbogun, M. S., Guerin, A., Nitulescu, R., Ramanakumar, A. B., Kamat, S. A., et al. (2016). The economic burden of schizophrenia in the United States in 2013. Journal of Clinical Psychiatry, 77, 764–771.

Coate, D., & Markowitz, S. (2004). The effects of daylight and daylight saving time on US pedestrian fatalities and motor vehicle occupant fatalities. Accident Analysis and Prevention, 36, 351–357.

Coccaro, E. F., Fanning, J. R., Phan, K. L., & Lee, R. (2015). Serotonin and impulsive aggression. CNS Spectrums, 20, 295–302.

Coccaro, E. F., Lee, R., Groer, M. W., Can, A., Coussons-Reed, M., & Postolache, T. T. (2016). *Taxoplasma gondii* infection: Relationship with aggression in psychiatric subjects. Journal of Clinical Psychiatry, 77, 334–341.

Coccaro, E. F., Sripada, C. S., Yanowitch, R. N., & Phan, K. L. (2011). Corticolimbic function in impulsive aggressive behavior. Biological Psychiatry, 69, 1153–1159.

Cochlear Limited. (2019, December 11). FDA clears Cochlear's innovative new Osia 2 hearing implant system. Cision PR

Newswire. Retrieved from https://www.prnewswire.com/news-releases/fda-clears-cochlears-innovative-new-osia-2-hearing-implant-system-300970910.html

Coffee and Caffeine Genetics Consortium, Cornelis, M. C., Byrne, E. M., Esko, T., Nalls, M. A., Ganna, A., et al. (2015). Genome-wide meta-analysis identifies six novel loci associated with habitual coffee consumption. Molecular Psychiatry, 20, 647–656.

Coffman, B. A., Trumbo, M. C., & Clark, V. P. (2012). Enhancement of object detection with transcranial direct current stimulation is associated with increased attention. BMC Neuroscience, 13, 108. Retrieved from http://www.biomedcentral.com/1471-2202/13/108.

Cohen, J. D., & Tong, F. (2001). The face of controversy. Science, 293, 2405–2407.

Cohen, L. G., Celnik, P., Pascual-Leone, A., Corwell, B., Faiz, L., Dambrosia, J., et al. (1997). Functional relevance of cross-modal plasticity in blind humans. Nature, 389, 180.

Cohen, M. X., Schoene-Bake, J.-C., Elger, C. E., & Weber, B. (2009). Connectivity-based segregation of the human striatum predicts personality characteristics. Nature Neuroscience, 12, 32–34.

Cohen, N. J., Eichenbaum, H., Deacedo, B. S., & Corkin, S. (1985). Different memory systems underlying acquisition of procedural and declarative knowledge. Annals of the New York Academy of Sciences, 444, 54–71.

Cohen, P., & Friedman, J. M. (2004). Leptin and the control of metabolism: Role for stearoyl-CoA desaturase-1 (SCD-1). Journal of Nutrition, 134, 2455S–2463S.

Cohen, S., Frank, E., Doyle, W. J., Skoner, D. P., Rabin, B. S., & Gwaltney, J. M., Jr. (1998). Types of stressors that increase susceptibility to the common cold in healthy adults. Health Psychology, 17, 214–223.

Cohen, S., Tyrrell, D. A., & Smith, A. P. (1991). Psychological stress and susceptibility to the common cold. New England Journal of Medicine, 325, 606–612.

Cohen-Kettenis, P. T. (2005). Gender change in 46 XY persons with 5-alpha-reductase-2 deficiency and 17-beta-hydroxysteroid dehydrogenase-3 deficiency. Archives of Sexual Behavior, 34, 399–410.

Colapinto, J. (2004, June 3). Gender gap: What were the real reasons behind David Reimer's suicide? Slate. Retrieved from www.slate.com/id/2101678

Colby, C. L., & Goldberg, M. E. (1999). Space and attention in parietal cortex. Annual Review of Neuroscience, 22, 319–349.

Coldeway, D. (2019, June 14). This neural network detects whether faces have been photoshopped. TechCrunch. Retrieved from https://techcrunch.com/2019/06/14/this-neural-network-detects-whether-faces-have-been-photoshopped

Cole, J. (1995). Pride and a daily marathon. Cambridge, MA: MIT Press.

Cole, S. W., Kemeny, M. E., Fahey, J. L., Zack, J. A., & Naliboff, B. D. (2003). Psychological risk factors for HIV pathogenesis: Mediation by the autonomic nervous system. Biological Psychiatry, 54, 1444–1456.

Coleman, D. L. (1973). Effects of parabiosis of obese with diabetes and normal mice. Diabetologia, 9, 294–298.

Coleman, D. L., & Hummel, K. P. (1969). Effects of parabiosis of normal with genetically diabetic mice. American Journal of Physiology, 217, 1298–1304.

Collaer, M. L., & Hines, M. (1995). Human behavioral sex differences: A role for gonadal hormones during early development? Psychological Bulletin, 118, 55–107.

Collaer, M. L., Reimers, S., & Manning, J. T. (2007). Visuospatial performance on an internet line judgment task and potential hormonal markers: Sex, sexual orientation, and 2D:4D. Archives of Sexual Behavior, 36, 177–192.

Colman, R. J., Beasley, T. M., Kemnitz, J. W., Johnson, S. C., Weindruch, R., & Anderson, R. M. (2014). Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. Nature Communications. doi:10.1038/ncomms557

Colt, E. W. D., Wardlaw, S. L., & Frantz, A. G. (1981). The effect of running on plasma β-endorphin. Life Sciences, 28, 1637–1640.

Columbia University. (n.d.). A study of the gene therapy CGF166 in patients with severe-to-profound hearing loss. Retrieved from https://www.entcolumbia.org/research/clinical-trials/find-clinical-trial/study-gene-therapy-cgf166-patients-severe-profound-hearing-loss

Considine, R. V., Sinha, M. K., Heiman, M. L., Kriauciunas, A., Stephens, T. W., Nyce, M. R., et al. (1996). Serum immunoreactive-leptin concentrations in normal-weight and obese humans. New England Journal of Medicine, 334, 292–295.

Constantinidis, C., & Steinmetz, M. A. (1996). Neuronal activity in posterior parietal area 7a during the delay periods of a spatial memory task. Journal of Neurophysiology, 76, 1352–1355.

Conway, B. R., & Livingstone, M. S. (2006). Spatial and temporal properties of cone signals in alert Macaque primary visual cortex. Journal of Neuroscience, 26, 10826–10846.

Cook, T. B., Brenner, L. A., Cloninger, C. R., Langenberg, P., Igbide, A., Giegling, I., et al. (2015). “Latent” infection with *Toxoplasma gondii*: Association with trait aggression and impulsivity in healthy adults. Journal of Psychiatric Research, 60, 87–94.

Cooke, S. F., & Bliss, T. V. P. (2006). Plasticity in the human central nervous system. Brain, 129, 1659–1673.

Coon, D. (2001). Introduction to psychology: Gateways to mind and behavior (with InfoTrac; 9th ed.). Belmont, CA: Wadsworth/Thomson Learning.

Corbetta, M., Miezin, F. M., Dobmeyer, S., Shulman, G. L., & Petersen, S. E. (1990). Attentional modulation of neural processing of shape, color, and velocity in humans. Science, 248, 1556–1559.

Cordone, S., Annarumma, L., Rossini, P. M., & De Gennaro, L. (2019). Sleep and β-amyloid deposition in Alzheimer disease: insights on mechanisms and possible innovative treatments. Frontiers in Pharmacology, 10, 695. Retrieved from https://www.frontiersin.org/articles/10.3389/fphar.2019.00695/full

Corkin, S. (1984). Lasting consequences of bilateral medial temporal lobectomy: Clinical course and experimental findings in H. M. *Seminars in Neurology*, 4, 249–259.

Corkin, S. (2002). What's new with the amnesic patient H. M.? Nature Reviews Neuroscience, 3, 153–160.

Corkin, S., Amaral, D. G., González, R. G., Johnson, K. A., & Hyman, B. T. (1997). HM's medial temporal lobe lesion: Findings from magnetic resonance imaging. Journal of Neuroscience, 17, 3964–3979.

Correll, C. U. (2010). From receptor pharmacology to improved outcomes: Individualising the selection, dosing, and switching of antipsychotics. European Psychiatry, 25, S12–S21.

Cortés-Cortés, J., Fernández, R., Teijeiro, N., Gómez-Gil, E., Esteva, I., Almaraz, M. C., et al. (2017). Genotypes and haplotypes of the estrogen receptor α gene (ESR1) are associated with female-to-male gender dysphoria. Journal of Sexual Medicine, 14, 464–472.

Corvol, J.-C., Artaud, F., Cormier-Dequaire, F., Rascol, O., Durif, F., Dekinderen, P., et al. (2018). Longitudinal analysis of impulse control disorders in Parkinson's disease. Neurology, 91, e189–e201. doi:10.1212/WNL.0000000000005816.

Cosgrove, G. R., & Eskandar, E. (1998). Thalamotomy and pallidotomy. Retrieved from https://www.neurosurgery.mgh.harvard.edu/functional/pallidt.htm

Cosmo, C., Ferreira, C., Miranda, J. G. V., do Rosário, R. S., Baptista, A. F., Montoya, P., & de Sena, E. P. (2015). Spreading effect of tDCS in individuals with attention-deficit/hyperactivity disorder as shown by functional cortical networks: A randomized, double-blind, sham-controlled trial. Frontiers in Psychiatry, 6, 111. doi:10.3389/fpsyt.2015.00111

Costa, G. de M. (2016). New insights into cortisol levels in PTSD. Brazilian Journal of Psychiatry, 38, 176.

Costall, B., & Naylor, R. J. (1992). Anxiolytic potential of 5-HT3 receptor antagonists. Pharmacology and Toxicology, 70, 157–162.

Courtet, P., Gottesman, L. L., Jollant, F., & Gould, T. D. (2011). The neuroscience of suicidal behaviors: What can we expect from endophenotype strategies? Translational Psychiatry, 1, e7. doi:10.1038/tp.2011.6

Courtney, S. M., Ungerleider, L. G., Keil, K., & Haxby, J. V. (1997). Transient and sustained activity in a distributed neural system for human working memory. Nature, 386, 608–611.

Court of Arbitration for Sport. (2019, April 30). Executive summary. Retrieved from https://www.tas-cas.org/fileadmin/user_upload/CAS_Executive_Summary__5794_.pdf

Cox, D. J., Merkel, R. L., Kovatchev, B., & Seward, R. (2000). Effect of stimulant medication on driving performance of young adults with attention-deficit/hyperactivity disorder: A preliminary double-blind placebo controlled trial. Journal of Nervous and Mental Disease, 188, 230–234.

Cox, J. J., Reimann, F., Nicholas, A. K., Thornton, G., Roberts, E., Springell, K., et al. (2006). An *SCN9A* channelopathy causes congenital inability to experience pain. Nature, 444, 894–898.

Coyle, J. T. (2006). Glutamate and schizophrenia: Beyond the dopamine hypothesis. Cellular and molecular neurobiology, 26, 365–384.

Craig, A. D. (2009). How do you feel—Now? The anterior insula and human awareness. Nature Reviews Neuroscience, 10, 59–70.

Craig, I. W., & Halton, K. E. (2009). Genetics of human aggressive behaviour. Human Genetics, 126, 101–113.

Crane, G. E. (1957). Iproniazid (Marsilid) phosphate, a therapeutic agent for mental disorders and debilitating diseases. Psychiatry Research Reports, 8, 142–152.

Crick, F. (1994). The astonishing hypothesis: The scientific search for the soul. New York, NY: Scribner.

Criminologist believes violent behavior is biological. (2013, April 30). NPR Books. Retrieved from http://www.npr.org/2013/05/01/180096559/criminologist-believes-violent-behavior-is-biological

Criss, D. (2019, April 19). Every year a Filipino man marks Good Friday with an actual crucifixion. He just did it for the 33rd time. CNN. Retrieved from https://www.cnn.com/2019/04/19/asia/philippines-crucifixion-practice-33rd-year-trnd

Croft, H. A. (2017). Understanding the role of serotonin in female hypoactive sexual desire disorder and treatment options. Journal of Sexual Medicine, 14, 1575–1584.

Cross-Disorder Group of the Psychiatric Genomics Consortium. (2013). Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. Lancet, 381, 1371–1379.

Crowe, R. R. (1984). Electroconvulsive therapy: A current perspective. New England Journal of Medicine, 311, 163–167.

Culham, J., He, S., Dukelow, S., & Verstraten, F. A. J. (2001). Visual motion and the human brain: What has neuroimaging told us?

Acta Psychologica, 107, 69–94.

Culp, R. E., Cook, A. S., & Housley, P. C. (1983). A comparison of observed and reported adult-infant interactions: Effects of perceived sex. Sex Roles, 9, 475–479.

Culverhouse, R. C., Saccone, N. L., Horton, A. C., Ma, Y., Anstey, K. J., Banaschewski, T., et al. (2018). Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression. Molecular Psychiatry, 23, 133–142.

Cummings, D. E., Clement, K., Purnell, J. Q., Vaisse, C., Foster, K. E., Frayo, R. S., et al. (2002). Elevated plasma ghrelin levels in Prader-Willi syndrome. Nature Medicine, 8, 643–644.

Cummings, D. E., Purnell, J. Q., Frayo, R. S., Schmidova, K., Wisse, B. E., & Weigle, D. S. (2001). A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes, 50, 1714–1719.

Curcio, C. A., Sloan, K. R., Kalina, R. E., & Hendrickson, A. E. (1990). Human photoreceptor topography. Journal of Comparative Neurology, 292(4), 497–523.

Currie, P. J., & Coscina, D. V. (1996). Regional hypothalamic differences in neuropeptide Y-induced feeding and energy substrate utilization. Brain Research, 737, 238–242.

Curtis, M. A., Penney, E. B., Pearson, A. G., van Roon-Mom, W. M. C., Butterworth, N. J., Dragunow, M., et al. (2003). Increased cell proliferation and neurogenesis in the adult human Huntington’s disease brain. Proceedings of the National Academy of Sciences, 100, 9023–9027.

Cuthbert, B. N. (2019). The PRISM project: Social withdrawal from an RDoC perspective. Neuroscience & Biobehavioral Reviews, 97, 34–37.

Cyranoski, D. (2016, November 15). CRISPR gene-editing tested in a person for the first time. Nature NEWS. Retrieved from https://www.nature.com/news/crispr-gene-editing-tested-in-a-person-for-the-first-time-1.20988

Cyranoski, D. (2019, February 26). The CRISPR-baby scandal: What's next for human gene-editing. Nature. Retrieved from https://www.nature.com/articles/d41586-019-00673-1

Czeisler, C. A., Duffy, J. F., Shanahan, T. L., Brown, E. N., Mitchell, J. F., Rimmer, D. W., et al. (1999). Stability, precision, and near-24-hour period of the human circadian pacemaker. Science, 284, 2177–2181.

Czeisler, C. A., Johnson, M. P., Duffy, J. F., Brown, E. N., Ronda, J. M., & Kronauer, R. E. (1990). Exposure to bright light and darkness to treat physiologic maladaptation to night work. New England Journal of Medicine, 322, 1253–1259.

Czeisler, C. A., Moore-Ede, M. C., & Coleman, R. M. (1982). Rotating shift work schedules that disrupt sleep are improved by applying circadian principles. Science, 217, 460–463.

Czeisler, C. A., Richardson, G. S., Coleman, R. M., Zimmerman, J. C., Moore-Ede, M. C., Dement, W. C., et al. (1981). Chronotherapy: Resetting the circadian clocks of patients with delayed sleep phase insomnia. Sleep, 4, 1–21.

Czeisler, C. A., Weitzman, E. D., & Moore-Ede, M. C. (1980). Human sleep: Its duration and organization depend on its circadian phase. Science, 210, 1264–1267.

Dabbs, J. M., Jr., Carr, T. S., Frady, R. L., & Riad, J. K. (1995). Testosterone, crime, and misbehavior among 692 male prison inmates. Personality and Individual Differences, 18, 627–633.

Dabbs, J. M., Jr., & Hargrove, M. F. (1997). Age, testosterone, and behavior among female prison inmates. Psychosomatic Medicine, 59, 477–480.

Dabbs, J. M., Jr., & Mohammed, S. (1992). Male and female salivary testosterone concentrations before and after sexual activity. Physiology and Behavior, 52, 195–197.

Dacey, D. M., Llao, H.-W., Peterson, B. B., Robinson, F. R., Smith, V. C., Pokorny, J., et al. (2005). Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. Nature, 433, 749–754.

da Cruz L., Fynes K., Georgiadis O., Kerby J., Luo Y., Ahmado A, et al. (2018). Phase 1 clinical study of an embryonic stem cell-derived retinal pigment epithelium patch in age-related macular degeneration. Nature Biotechnology, 36, 328–337.

Dahlhamer, J., Lucas, J., Zelaya, C., Nahin, R., Mackey, S. DeBar, L., et al. (2016). Prevalence of chronic pain and high-impact chronic pain among adult—United States. MMWR and Morbidity and Mortality Weekly Report, 67, 1001–1006.

Dalla Barba, G., & La Corte, V. (2015). A neurophenomenological model for the role of the hippocampus in temporal consciousness. Evidence from confabulation. Frontiers in Behavioral Neuroscience, 9, 218. Retrieved from https://www.frontiersin.org/articles/10.3389/fnbeh.2015.00218/full

Dalsager, L., Fage-Larsen, B., Bilenberg, N., Jensen, T. K., Nielsen, F., Kyhl, H. B., et al. (2019). Maternal urinary concentrations of pyrethroid and chlorpyrifos metabolites and attention deficit

hyperactivity disorder (ADHD) symptoms in 2-4-year-old children from the Odense Child Cohort. Environmental Research, 176, 108533. Retrieved from https://europepmc.org/article/med/31229776

Dalsgaard, S., Nielsen, H. S., & Simonsen, M. (2013). Five-fold increase in national prevalence rates of attention-deficit hyperactivity disorder medications for children and adolescents with autism spectrum disorder, attention-deficit/hyperactivity disorder, and other psychiatric disorders: A Danish register-based study. Journal of Child and Adolescent Psychopharmacology, 23, 432–439.

Dalsgaard, S., Østergaard, S. D., Leckman, J. F., Mortensen, P. B., & Pedersen, M. G. (2015). Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: A nationwide cohort study. Lancet, 385, 2190–2196.

Dalton, A. (2005, May/June). Sleepstalking: A child molester pleads unconsciousness. Legal Affairs. Retrieved from https://www.legalaffairs.org/issues/May-June-2005/scene_dalton_mayjun05.msp

Dalton, R. (2000). NIH cash tied to compulsory training in good behavior. Nature, 408, 629.

Daly, M., & Wilson, M. (1988). Homicide. New York, NY: Aldine de Gruyter.

Damasio, A. (1994). Descartes' error: Emotion, reason, and the human brain. New York, NY: Putnam.

Damasio, A. R. (1985). Prosopagnosia. Trends in Neurosciences, 8, 132–135.

Damasio, H., Grabowski, T., Frank, R., Galaburda, A. M., & Damasio, A. R. (1994). The return of Phineas Gage: Clues about the brain from the skull of a famous patient. Science, 264, 1102–1105.

Damasio, H., Grabowski, T. J., Tranel, D., Hichwa, R. D., & Damasio, A. R. (1996). A neural basis for lexical retrieval. Nature, 380, 499–505.

Dandy, J., & Nettelbeck, T. (2002). The relationship between IQ, homework, aspirations and academic achievement for Chinese, Vietnamese and Anglo-Celtic Australian school children. Educational Psychology, 22, 267–276.

Daneschvar, H. L., Aronson, M. D., & Smetana, G. W. (2016). FDA-approved anti-obesity drugs in the United States. American Journal of Medicine, 129, 879.e1-6. doi:10.1016/j.amjmed.2016.02.009.

Dang-Vu, T. T., McKinney, S. M., Buxton, O. M., Solet, J. M., & Ellenbogen, J. M. (2010). Spontaneous brain rhythms predict sleep stability in the face of noise. Current Biology, 20, R626–R627.

Daniel, D., Weinberger, D. R., Jones, D. W., Zigun, J. R., Coppola, R., Handel, S., et al. (1991). The effect of amphetamine on regional cerebral blood flow during cognitive activation in schizophrenia. Journal of Neuroscience, 11, 1907–1917.

Dapretto, M., Davies, M. S., Pfeifer, J. H., Scott, A. A., Sigman, M., Bookheimer, S. Y., et al. (2005). Understanding emotions in others: Mirror neuron dysfunction in children with autism spectrum disorders. Nature Neuroscience, 9, 28–30.

Darling, R. A., Zhao, H., Kinch, D., Li, A. J., Simasko, S. M., & Ritter, S. (2014). Mercaptoacetate and fatty acids exert direct and

antagonistic effects on nodose neurons via GPR40 fatty acid receptors. American Journal of Physiology—Regulatory, Integrative and Comparative Physiology, 307, R35–R43.

Dartnall, H. J. A., Bowmaker, J. K., & Mollon, J. D. (1983). Human visual pigments: Microspectrophotometric results from the eyes of seven persons. Proceedings of the Royal Society of London, B, 220, 115–130.

Darwin, C. (1859). On the origin of species. London, UK: Murray.

Darwin, C. (1871). The descent of man and selection in relation to sex. London, UK: Murray.

Das, A., & Gilbert, C. D. (1995). Long-range horizontal connections and their role in cortical reorganization revealed by optical recording of cat primary visual cortex. Nature, 375, 780–784.

Das, R. K., Gale, G., Walsh, K., Hennessy, V. E., Iskandar, G., Brandner, B., et al. (2019). Ketamine can reduce harmful drinking by pharmacologically rewriting drinking memories. Nature Communications, 10, Article 5187. Retrieved from https://www.nature.com/articles/s41467-019-13162-w

Davatzikos, C., Wolf, D. H., Koutsouleris, N., Satterthwaite, T. D., Gur, R. E., Gur, R. C., et al. (2020). Two distinct neuroanatomical subtypes of schizophrenia revealed using machine learning. Brain, 143, 1027–1038.

David, A. S., & Prince, M. (2005). Psychosis following head injury: A critical review. Journal of Neurology and Neurosurgical Psychiatry, 76, i53–i60.

Davidson, J. M. (1966). Characteristics of sex behavior in male rats following castration. Animal Behavior, 14, 266–272.

Davidson, R. J., Pizzagalli, D., Nitschke, J. B., & Putnam, K. (2002). Depression: Perspectives from affective neuroscience. Annual Review of Psychology, 53, 545–574.

Davies, K. (2019, January 21). He Jiankui fired in wake of CRISPR babies investigation. Genetic Engineering & Biotechnology News. Retrieved from https://www.genengnews.com/news/he-jiankui-fired-in-wake-of-crispr-babies-investigation

Davis, C. M. (1928). Self selection of diet in newly weaned infants: An experimental study. American Journal of Diseases of Children, 36, 651–679.

Davis, J. O., Phelps, J. A., & Bracha, H. S. (1995). Prenatal development of monozygotic twins and concordance for schizophrenia. Schizophrenia Bulletin, 21, 357–366.

Davis, K. D., Hutchison, W. D., Lozano, A. M., Tasker, R. R., & Dostrovsky, J. O. (2000). Human anterior cingulate cortex neurons modulated by attention-demanding tasks. Journal of Neurophysiology, 83, 3575–3577.

Davis, R. L. & Zhong, Y. (2017). The biology of forgetting—A perspective. Neuron, 95, 490–503.

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2008). Qué PASA? The posterior-anterior shift in aging. Cerebral Cortex, 18, 1201–1209.

Deacon, T. W. (1990). Rethinking mammalian brain evolution. American Zoologist, 30, 629–705.

Dean, D. C., III, Jerskey, B. A., Chen, K., Protas, H., Thiyagura, P., Roontiva, A., et al. (2014). Brain differences in infants at

differential genetic risk for late-onset Alzheimer disease: A cross-sectional imaging study. JAMA Neurology, 71, 11–22.

Dealberto, M.-J. (2013). Are the rates of schizophrenia unusually high in Canada? A comparison of Canadian and international data. Psychiatry Research, 209, 259–265.

Deary, I. J., Strand, S., Smith, P., & Fernandes, C. (2007). Intelligence and educational achievement. Intelligence, 35, 13–21.

deCharms, R. C., Maeda, F., Glover, G. H., Ludlow, D., Pauly, J. M., Soneji, D., et al. (2005). Control over brain activation and pain learned by using real-time functional MRI. Proceedings of the National Academy of Sciences, 102, 18626–18631.

Dediu, D., & Levinson, S. C. (2013). On the antiquity of language: The reinterpretation of Neandertal linguistic capacities and its consequences. Frontiers in Psychology, 4, Article 397. Retrieved from http://www.frontiersin.org/Language_Sciences/10.3389/fpsyg.2013.00397/abstract

Deer, B. (2011). How the case against the MMR vaccine was fixed. British Medical Journal, 342, c5347. Retrieved from http://www.bmj.com/content/342/bmj.c5347

de Gelder, B., & Tamietto, M. (2007). Affective blindsight. Scholarpedia, 2, 3555. Retrieved from https://www.scholarpedia.org/article/Affective_blindsight

de Gonzalez, A. B., Hartge, P., Cerhan, J. R., Flint, A. J., Hannan, L., Cerhan, J. R., et al. (2010). Body-mass index and mortality among 1.46 million white adults. New England Journal of Medicine, 363, 2211–2219.

Degreef, G., Ashtari, M., Bogerts, B., Bilder, R. M., Jody, D. N., Alvir, J., et al. (1992). Volumes of ventricular system subdivisions measured from magnetic resonance images in first-episode schizophrenic patients. Archives of General Psychiatry, 49, 531–537.

de Haan, S., Rietveld, E., Stokhof, M., & Denys, D. (2015). Effects of deep brain stimulation on the lived experience of obsessive-compulsive disorder patients: In-depth interviews with 18 patients. PLoS One, 10, e0135524.

Dehaene, S. (1997). The number sense: How the mind creates mathematics. New York, NY: Oxford University Press.

Dehaene, S. (2009). Reading in the brain: The science and evolution of a human invention. New York, NY: Viking.

Dehaene, S., & Cohen, L. (1997). Cerebral pathways for calculation: Double dissociation between rote verbal and quantitative knowledge of arithmetic. Cortex, 33, 219–250.

Dehaene, S., & Naccache, L. (2001). Towards a cognitive neuroscience of consciousness: Basic evidence and a workspace framework. Cognition, 79, 1–37.

Dehaene, S., Naccache, L., Cohen, L., Le Bihan, D., Mangin, J.-F., Poline, J.-B., et al. (2001). Cerebral mechanisms of word masking and unconscious repetition priming. Nature Neuroscience, 4, 752–758.

Dehaene, S., Spelke, E., Pinel, P., Stanescu, R., & Tsivkin, S. (1999). Sources of mathematical thinking: Behavioral and brain-imaging evidence. Science, 284, 970–974.

Deisseroth, K. (2015). Optogenetics: 10 years of microbial opsins in neuroscience. Nature Neuroscience, 18, 1213–1225.

de Jager, C. A., Oulhaj, A., Jacoby, R., Refsum, H., & Smith, A. D. (2012). Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: A randomized controlled trial. International Journal of Geriatric Psychiatry, 27, 592–600.

De Jager, P. L., Srivastava, G., Lunnon, K., Burgess, J., Schalkwyk, L. C., Yu, L., et al. (2014). Alzheimer's disease: Early alterations in brain DNA methylation at *ANK1, BIN1, RHBDF2*, and other loci. Nature Neuroscience, 17, 1156–1163.

de Jonge, F. H., Louwerse, A. L., Ooms, M. P., Evers, P., Endert, E., & Van de Poll, N. E. (1989). Lesions of the SDN-POA inhibit sexual behavior of male Wistar rats. Brain Research Bulletin, 23, 483–492.

de Jonge, F. H., Oldenburger, W. P., Louwerse, A. L., & Van de Poll, N. E. (1992). Changes in male copulatory behavior after sexual exciting stimuli: Effects of medial amygdala lesions. Physiology and Behavior, 52, 327–332.

Dekker, A. D., De Deyn, P. P., & Rots, M. G. (2014). Epigenetics: The neglected key to minimize learning and memory deficits in Down syndrome. Neuroscience and Biobehavioral Reviews, 45, 72–84.

de la Fuente-Fernández, R., Ruth, T. J., Sossi, V., Schulzer, M., Calne, D. B., & Stoessl, A. J. (2001). Expectation and dopamine release: Mechanism of the placebo effect in Parkinson's disease. Science, 293, 1164–1166.

Dell'Amore, C. (2019, October 4). Pigs recorded using tools for the first time. National Geographic. Retrieved from

https://www.nationalgeographic.com/animals/2019/10/first-tool-use-pigs-visayan-endangered

DeLuca, G. C., Ebers, G. C., & Esiri, M. M. (2004). Axonal loss in multiple sclerosis: A pathological survey of the corticospinal and sensory tracts. Brain, 127, 1009–1018.

De Luca, V., Wang, H., Squassina, A., Wong, G. W. H., Yeomans, J., & Kennedy, J. L. (2004). Linkage of M5 muscarinic and a7-nicotinic receptor genes on 15q13 to schizophrenia. Neuropsychobiology, 50, 124–127.

Dement, W. (1960). The effect of dream deprivation. Science, 131, 1705–1707.

De Meyer, G., Shapiro, F., Vanderstichele, H., Vanmechelen, E., Engelborghs, S., De Deyn, P. P., et al. (2010). Diagnosis-independent Alzheimer disease biomarker signature in cognitively normal elderly people. Archives of Neurology, 67, 949–956.

Demicheli, V., Jefferson, T., Rivetti, A., & Price, D. (2005). Vaccines for measles, mumps and rubella in children. Cochrane Database of Systematic Reviews. Retrieved from https://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004407/frame.html

Dempster, E., Viana, J., Pidsley, R., & Mill, J. (2013). Epigenetic studies of schizophrenia: Progress, predicaments, and promises for the future. Schizophrenia Bulletin, 39, 11–16.

den Hollander, B., Schouw, M., Groot, P., Huisman, H., Caan, M., Barkhof, F., & Reneman, L. (2012). Preliminary evidence of hippocampal damage in chronic users of ecstasy. Journal of Neurology, Neurosurgery, and Psychiatry, 83, 83–85.

Denson, T. F., O'Dean, S. M., Blake, K. R., & Beames, J. R. (2018). Aggression in women: Behavior, brain and hormones. Frontiers in Behavioral Neuroscience, 12, 81. Retrieved from https://www.frontiersin.org/articles/10.3389/fnbeh.2018.00081/full

Denyer, R., & Douglas, M. R. (2012). Gene therapy for Parkinson's disease. Parkinson's Disease, 2012, Article ID 757305.

Deol, M. S., & Gluecksohn-Waelsch, S. (1979). The role of inner hair cells in hearing. Nature, 278, 250–252.

Depression Guideline Panel. (1993). Clinical practice guideline number 5: Depression in primary care II (AHRQ Publication No. 93-0551). Rockville, MD: U.S. Department of Health and Human Services.

Depue, R. A., & Iacono, W. G. (1989). Neurobehavioral aspects of affective disorders. Annual Review of Psychology, 40, 457–492.

DeSantis, A. D., Webb, E. M., & Noar, S. M. (2008). Illicit use of prescription ADHD medications on a college campus: A multimethodological approach. Journal of American College Health, 57, 315–324.

Descartes, R. (1984). Treatise on man (J. Cottingham, R. Stoothoff, & D. Murdoch, Trans.). The philosophical writings of Descartes. New York, NY: Cambridge University Press. (Original work published about 1662)

De Silva, A., & Bloom., S. R. (2012). Gut hormones and appetite control: A focus on PYY and GLP-1 as therapeutic targets in obesity. Gut and Liver, 6, 10–20.

Desimone, R., Albright, T. D., Gross, C. G., & Bruce, C. (1984). Stimulus-selective properties of inferior temporal neurons in the

macaque. Journal of Neuroscience, 4, 2051–2062.

D'Esposito, M., & Postle, B. R. (1999). The dependence of span and delayed response performance on prefrontal cortex. Neuropsychologia, 37, 1303–1315.

Desrivières, S., Lourdusamy, A., Tao, C., Toro, R., Jia, T., Loth, E., et al. (2014). Single nucleotide polymorphism in the neuroplastin locus associates with cortical thickness and intellectual ability in adolescents. Molecular Psychiatry. doi:10.1038/mp.2013.197

Dessens, A. B., Slijper, F. M. E., & Drop, S. L. S. (2005). Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. Archives of Sexual Behavior, 34, 389–397.

De Stefano, N., Matthews, P. M., Filippi, M., Agosta, F., De Luca, M., Bartolozzi, M. L., et al. (2003). Evidence of early cortical atrophy in MS. Neurology, 60, 1157–1162.

Deutsch, S. I., Rosse, R. B., Schwartz, B. L., Weizman, A., Chilton, M., Arnold, D. S., et al. (2005). Therapeutic implications of a selective a7 nicotinic receptor abnormality in schizophrenics. Israeli Journal of Psychiatry and Related Sciences, 42, 33–44.

De Valois, R. L. (1960). Color vision mechanisms in the monkey. Journal of General Physiology, 43, 115–128.

De Valois, R. L., Abramov, I., & Jacobs, G. H. (1966). Analysis of response patterns of LGN cells. Journal of the Optical Society of America, 56, 966–977.

De Valois, R. L., Thorell, L. G., & Albrecht, D. G. (1985). Periodicity of striate-cortex-cell receptive fields. Journal of the Optical Society of America, 2, 1115–1123.

Devanand, D. P., Dwork, A. J., Hutchinson, E. R., Bolwig, T. G., & Sackeim, H. A. (1994). Does ECT alter brain structure? American Journal of Psychiatry, 151, 957–970.

Devane, W. A., Hanus, L., Breuer, A., Pertwee, R. G., Stevenson, L. A., Griffin, G., et al. (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science, 258, 1946–1949.

Devitt, M. (2018, December 10). CDC data show U.S. life expectancy continues to decline. AAFP News. Retrieved from https://www.aafp.org/news/health-of-the-public/20181210lifeexpectdrop.html

de Vivo, L., Bellesi, M., Marshall, W., Bushong, E. A., Ellisman, M. H., Tononi, G., & Cirelli, C. (2017). Ultrastructural evidence for synaptic scaling across the wake/sleep cycle. Science, 355, 507–510.

Devlin, B., Daniels, M., & Roeder, K. (1997). The heritability of IQ. Nature, 388, 468–471.

Devue, C., Collette, F., Balteau, E., Degueldre, C., Luxen, A., Maquet, P., et al. (2007). Here I am: The cortical correlates of visual self-recognition. Brain Research, 1143, 169–182.

Dew, M. A., Reynolds, C. F., III, Buysse, D. J., Houck, P. R., Hoch, C. C., Monk, T. H., et al. (1996). Electroencephalographic sleep profiles during depression: Effects of episode duration and other clinical and psychosocial factors in older adults. Archives of General Psychiatry, 53, 148–156.

Deweerdt, S. (2019, May 1). The signaling imbalance theory of autism, explained. Spectrum News. Retrieved from https://www.spectrumnews.org/news/signaling-imbalance-theory-autism-explained

DeWitt, S. J., Aslan, S., & Filbey, F. M. (2014). Adolescent risk-taking and resting state functional connectivity. Psychiatry Research: Neuroimaging, 222, 157–164.

Dewsbury, D. A. (1981). Effects of novelty on copulatory behavior: The Coolidge effect and related phenomena. Psychological Bulletin, 89, 464–482.

Dhond, R. P., Buckner, R. L., Dale, A. M., Marinkovic, K., & Halgren, E. (2001). Spatiotemporal maps of brain activity underlying word generation and their modification during repetition priming. Journal of Neuroscience, 21, 3564–3571.

Diamond, J. (1992). Turning a man. Discover, 13, 71–77.

Diamond, M. (1965). A critical evaluation of the ontogeny of human sexual behavior. Quarterly Review of Biology, 40, 147–175.

Diamond, M., & Sigmundson, H. K. (1997). Sex reassignment at birth: Long-term review and clinical implications. Archives of Pediatric and Adolescent Medicine, 151, 298–304.

Diamond, M. C., Scheibel, A. B., Murphy, G. M., Jr., & Harvey, T. (1985). On the brain of a scientist: Albert Einstein. Experimental Neurology, 88, 198–204.

DiazGranados, N., & Zarate, C. A. (2008). A review of the preclinical and clinical evidence for protein kinase C as a target for drug development for bipolar disorder. Current Psychiatry Reports, 10, 510–519.

Dick, D., & Agrawal, A. (2008). The genetics of alcohol and other drug dependence. Alcohol Research and Health, 31, 111–118.

Dickson, D. A., Paulus, J. K., Mensah, V., Lem, J., Saavedra-Rodriguez, L, Gentry, A., et al. (2018). Reduced levels of miRNAs 449 and 34 in sperm of mice and men exposed to early life stress. Translational Psychiatry, 8, 101. Retrieved from https://www.nature.com/articles/s41398-018-0146-2

Diderot, D. (1916). Letter on the blind for the use of those who see. In M. Jourdain (Ed. and Trans.), Diderot's early philosophical works. Chicago, IL: Open Court. (Original work published 1749)

Diéguez, C., Frühbeck, G., & López, M. (2009). Hypothalamic lipids and the regulation of energy homeostasis. Obesity Facts, 2, 126-135.

Dietis, N., Guerrini, R., Calo, G., Salvadori, S., Rowbotham, D. J., & Lambert, D. G. (2009). Simultaneous targeting of multiple opioid receptors: A strategy to improve side-effect profile. British Journal of Anesthesia, 103, 38–49.

Dietrich, T., Krings, T., Neulen, J., Willmes, K., Erberich, S., Thron, A., et al. (2001). Effects of blood estrogen level on cortical activation patterns during cognitive activation as measured by functional MRI. NeuroImage, 13, 425–432.

Dietz, V. (2009). Body weight supported gait training: From laboratory to clinical setting. Brain Research Bulletin, 78, i–vi.

DiFiglia, M., Sapp, E., Chase, K. O., Davies, S. W., Bates, G. P., Vonsattel, J. P., et al. (1997). Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. Science, 277, 1990–1993.

Di Lorenzo, P. M., & Hecht, G. S. (1993). Perceptual consequences of electrical stimulation in the gustatory system. Behavioral Neuroscience, 107, 130–138.

Dilsaver, S. C. (2011). An estimate of the minimum economic burden of bipolar I and II disorders in the United States: 2009. Journal of Affective Disorders, 129, 79–83.

Di Martino, A., Yan, C.-G., Li, Q., Denio, E., Castellanos, F. X., Alaerts, K., et al. (2014). The autism brain imaging data exchange: Towards large-scale evaluation of the intrinsic brain architecture in autism. Molecular Psychiatry, 19, 659–667.

Di Marzo, V., Ligresti, A., & Cristino, L. (2009). The endocannabinoid system as a link between homeostatic and hedonic pathways involved in energy balance regulation. International Journal of Obesity, 33, S18–S24.

Dimitrijevic, M. R., Gerasimenko, Y., & Pinter, M. M. (1998). Evidence for a spinal central pattern generator in humans. Annals of the New York Academy of Sciences, 860, 360–376.

Dimond, Y., Schuetze, M., Smith, R. E., Dhollander, T., Cho, I., Vinetee, S., et al. (2019). Reduced white matter fiber density in autism spectrum disorder. Cerebral Cortex, 29(4), 1778–1788. Retrieved from https://academic.oup.com/cercor/article/29/4/1778/5298366

di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., & Rizzolatti, G. (1992). Understanding motor events: A neurophysiological study. Experimental Brain Research, 91, 176–180.

di Pellegrino, G., & Wise, S. P. (1993). Effects of attention on visuomotor activity in the premotor and prefrontal cortex of a primate. Somatosensory and Motor Research, 10, 245–262.

di Tomaso, E., Beltramo, M., & Piomelli, D. (1996). Brain cannabinoids in chocolate. Nature, 382, 677–678.

Dkhissi-Benyahya, O., Rieux, C., Hut, R. A., & Cooper, H. M. (2006). Immunohistochemical evidence of a melanopsin cone in human retina. Investigative Ophthalmology & Visual Science, 47, 1636–1641.

Doi, D., Morizane, A., Kikuchi, T., Onoe, H., Hayashi, T., Kawasaki, T., et al. (2012). Prolonged maturation culture favors a reduction in the tumorigenicity and the dopaminergic function of human ESC-derived neural cells in a primate model of Parkinson's disease. Stem Cells, 30, 935–945.

Dollfus, S., Everitt, B., Ribeyre, J. M., Assouly-Besse, F., Sharp, C., & Petit, M. (1996). Identifying subtypes of schizophrenia by cluster analysis. Schizophrenia Bulletin, 22, 545–555.

Dom, G., Sabbe, B., Hulstijn, W., & van den Brink, W. (2005). Substance use disorders and the orbitofrontal cortex: Systematic review of behavioural decision-making and neuroimaging studies. British Journal of Psychiatry, 187, 209–220.

Dombeck, D. A., Khabbaz, A. N., Collman, F., Adelman, T. L., & Tank, D. W. (2007). Imaging large-scale neural activity with cellular resolution in awake, mobile, mice. Neuron, 56, 43–57.

Dominguez, J. M., & Hull, E. M. (2001). Stimulation of the medial amygdala enhances medial preoptic dopamine release: Implications for male rat sexual behavior. Brain Research, 917, 225–229.

Donnay, G. F., Rankin, S. K., Lopez-Gonzalez, M., Jiradejvong, P., & Limb, C. J. (2014). Neural substrates of interactive musical improvisation: An fMRI study of "Trading Fours" in jazz. PLOS One, 9(2), e88665.

Dörner, G. (1974). Sex-hormone-dependent brain differentiation and sexual functions. In G. Dörner (Ed.), Endocrinology of sex (pp. 30–

37). Leipzig, Germany: J. A. Barth.

do Rosario-Campos, M. C., Leckman, J. F., Curi, M., Quatrano, S., Katsovitch, L., Miguel, E. C., et al. (2005). A family study of early-onset obsessive-compulsive disorder. American Journal of Medical Genetics, Part B, 136, 92–97.

Douaud, G., Refsum, H., de Jager, C. A., Jacoby, R., Nichols, T. E., Smith, S. M., & Smith, A. D. (2013). Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. Proceedings of National Academy of Sciences, 110, 9523–9528.

Doucleff, M. (2013, September 17). Auto-brewery syndrome: Apparently you can make beer in your gut. NPR. Retrieved from http://www.npr.org/sections/thesalt/2013/09/17/223345977/auto-brewery-syndrome-apparently-you-can-make-beer-in-your-gut

Doughty, C. J., Wells, J. E., Joyce, P. R., Olds, R. J., & Walsh, A. E. (2004). Bipolar-panic disorder comorbidity within bipolar disorder families: A study of siblings. Bipolar Disorders, 6, 245–252.

Dowell, D., Haegerich, T. M., & Chou, R. (2016). CDC Guideline for prescribing opioids for chronic pain—United States. Morbidity and Mortality Weekly Report, 65, 1–49. doi:10.15585/mmwr.rr6501e1

Dowling, J. E., & Boycott, B. B. (1966). Organization of the primate retina. Proceedings of the Royal Society of London, B, 166, 80–111.

Downing, P. E., Jiang, Y., Shuman, M., & Kanwisher, N. (2001). A cortical area selective for visual processing of the human body. Science, 293, 2470–2473.

Dreifus, C. (1996, February 4). And then there was Frank. New York Times Magazine, 23–25.

Drevets, W. C. (2001). Neuroimaging and neuropathological studies of depression: Implications for the cognitive-emotional features of mood disorders. Current Opinion in Neurobiology, 11, 240–249.

Drevets, W. C., Price, J. L., Simpson, J. R., Todd, R. D., Reich, T., Vannier, M., et al. (1997). Subgenual prefrontal cortex abnormalities in mood disorders. Nature, 386, 824–827.

Drevets, W. C., & Raichle, M. E. (1995). Positron emission tomographic imaging studies of human emotional disorders. In M. S. Gazzaniga (Ed.), The cognitive neurosciences (pp. 1153–1164). Cambridge, MA: MIT Press.

Drevets, W. C., Videen, T. O., Price, J. L., Preskorn, S. H., Carmichael, S. T., & Raichle, M. E. (1992). A functional anatomical study of unipolar depression. Journal of Neuroscience, 12, 3628–3641.

Driver, J., & Mattingley, J. B. (1998). Parietal neglect and visual awareness. Nature Neuroscience, 1, 17–22.

Drug Enforcement Administration. (2018). Justice Department, DEA propose significant opioid manufacturing reduction in 2019. Retrieved from https://www.dea.gov/press-releases/2018/08/16/justice-department-dea-propose-significant-opioid-manufacturing-reduction

Drumi, C. (2009). Stem cell research: Toward greater unity in Europe? Cell, 139, 649–651.

Dryden, S., Wang, O., Frankish, H. M., Pickavance, L., & Williams, G. (1995). The serotonin (5-HT) antagonist methysergide increases neuropeptide Y (NPY) synthesis and secretion in the hypothalamus of the rat. Brain Research, 699, 12–18.

Dudai, Y. (2004). The neurobiology of consolidations, or, how stable is the engram? Annual Review of Psychology, 55, 51–86.

Dudley, R. (2002). Fermenting fruit and the historical ecology of ethanol ingestion: Is alcoholism in modern humans an evolutionary hangover? Addiction, 97, 381–388.

Dufner-Almeida, L. G., da Cruz. D. B., Netto, R. C., M., Batissoco, A. C., Oiticica, J., & Salazar-Silva, R. (2019). Stem-cell therapy for hearing loss: are we there yet? Brazilian Journal of Otorhinolaryngology, 85, 520–529.

Dujardin, K., Guerrien, A., & Leconte, P. (1990). Sleep, brain activation and cognition. Physiology and Behavior, 47, 1271–1278.

Duncan, J., Seitz, R. J., Kolodny, J., Bor, D., Herzog, H., Ahmed, A., et al. (2000). A neural basis for general intelligence. Science, 289, 457–460.

Dunn, E. C., Brown, R. C., Dai, Y., Rosand, J., Nugent, N. R., Amstadter, A. B., et al. (2015). Genetic determinants of depression: Recent findings and future directions. Harvard Review of Psychiatry, 23, 1–18.

Durand, J.-B., Nelissen, K., Joly, O., Wardak, C., Todd, J. T., Norman, J. F., et al. (2007). Anterior regions of monkey parietal cortex process visual 3D shape. Neuron, 55, 493–505.

Durand, V. M., & Barlow, D. H. (2006). Essentials of abnormal psychology (4th ed.). Belmont, CA: Thomson Wadsworth.

Durso, G. R. O., Luttrell, A., & Way, B. M. (2015). Over-the-counter relief from pains and pleasures alike: Acetaminophen blunts evaluation sensitivity to both negative and positive stimuli. Psychological Science, 26, 750–758.

Dutton, D. G., & Aron, A. P. (1974). Some evidence for heightened sexual attraction under conditions of high anxiety. Journal of Personality and Social Psychology, 30, 510–517.

Dworak, M., McCarley, R. W., Kim, T., Kalinchuk, A. V., & Basheer, R. (2010). Sleep and brain energy levels: ATP changes during sleep. Journal of Neuroscience, 30, 9007–9016.

Earnest, D. J., Liang, F.-Q., Ratcliff, M., & Cassone, V. M. (1999). Immortal time: Circadian clock properties of rat suprachiasmatic cell lines. Science, 283, 693–695.

Eaton, W. W., Martins, S. S., Nestadt, G., Bienvenu, O. J., Clarke, D., & Alexandre, P. (2008). The burden of mental disorders. Epidemiology Review, 30, 1–14.

Eccard, J. A., Dammhahn, M., & Ylönen, H. (2017). The Bruce effect revisited: Is pregnancy termination in female rodents an adaptation to ensure breeding success after male turnover in low densities? Oecologia, 185, 81–94.

Eddy, K. T., Tabri, N., Thomas, J. J., Murray, H. B., Keshaviah, A., Hastings, E., et al. (2017). Recovery from anorexia nervosa and bulimia nervosa at 22-year follow-up. Journal of Clinical Psychiatry, 78, 184–189.

Edgerton, V. R., & Roy, R. R. (2009). Robotic training and spinal cord plasticity. Brain Research Bulletin, 78, 4–12.

Edlow, B. L., Chatelle, C., Spencer, C. A., Chu, C. J., Bodien, Y. G., O'Connor, K. L., et al. (2017). Early detection of consciousness in patients with acute severe traumatic brain injury. Brain. 140, 2399–2414.

Edwards, T. L., Cottriall, C. L., Xue, K., Simunovic, M. P., Ramsden, J. D., Zrenner, E., & MacLaren, R. E. (2018). Assessment of the electronic retinal implant Alpha AMS in restoring vision to blind patients with end-stage retinitis pigmentosa. Ophthalmology, 125, 432–443.

Egger, K., Schocke, M., Weiss, E., Auffinger, S., Esterhammer, R., Goebel, G., et al. (2008). Pattern of brain atrophy in elderly patients with depression revealed by voxel-based morphometry. Psychiatry Research, 164, 237–244.

Ehrhardt, A. A., Meyer-Bahlburg, H. F. L., Rosen, L. R., Feldman, J. F., Veridiano, N. P., Zimmerman, I., & McEwen, B. S. (1985). Sexual orientation after prenatal exposure to exogenous estrogen. Archives of Sexual Behavior, 14, 57–77.

Ehrsson, H. H., Spence, C., & Passingham, R. E. (2004). That's my hand! Activity in premotor cortex reflects feeling of ownership of a limb. Science, 305, 875–877.

Einarsdottir, E., Carlsson, A., Minde, J., Toolanen, G., Svensson, O., Solders, G., et al. (2004). A mutation in the nerve growth factor beta gene *(NGFB)* causes loss of pain perception. Human Molecular Genetics, 13, 799–805.

Eisenegger, C., Haushofer, J., & Fehr, E. (2011). The role of testosterone in social interaction. Cell, 15, 263–271.

Eksioglu, Y. Z., Scheffer, I. E., Cardenas, P., Knoll, J., DiMario, F., Ramsby, G., et al. (1996). Periventricular heterotopia: An x-linked dominant epilepsy locus causing aberrant cerebral cortical development. Neuron, 16, 77–87.

Elia, J., Gai, E. J., Xie, H. M., Perin, J. C., Geiger, E., Glessner, J. T., et al. (2010). Rare structural variants found in attention-deficit

hyperactivity disorder are preferentially associated with neurodevelopmental genes. Molecular Psychiatry, 15, 637–646.

Elias, M. (2008, May 13). Another person with super-memory skills comes forward. USA Today. Retrieved from https://www.usa-today.com/news/health/2008-05-12-super-memory_N.htm

Elks, C. E., den Hoed, M., Zhao, J. H., Sharp, S. J., Wareham, N. J., Loos, R. J. F., & Ong, K. K. (2012). Variability in the heritability of body mass index: A systematic review and meta-regression. Frontiers in Endocrinology, 3, 1–16.

Ellis, L., & Ames, M. A. (1987). Neurohormonal functioning and sexual orientation: A theory of homosexuality-heterosexuality. Psychological Bulletin, 101, 233–258.

Ellison-Wright, I., & Bullmore, E. (2009). Meta-analysis of diffusion tensor imaging studies in schizophrenia. Schizophrenia Research, 108, 3–10.

Elman, J. A., Oh, H., Madison, C. M., Baker, S. I., Vogel, J. W., Marks, S. M., et al. (2014). Neural compensation in older people with brain amyloid-b deposition. Nature Neuroscience, 17, 1316–1318.

El Marroun, H., Schmidt, M. N., Franken, I. H. A., Jaddoe, V. W. V., Hofman, A., van der Lugt, A., et al. (2013). Prenatal tobacco exposure and brain morphology: A prospective study in young children. Neuropsychopharmacology, 39, 792–800.

EMOTIV. (n.d.). EMOTIV EPOC+. Retrieved from https://www.emotiv.com/epoc

Enard, W., Khaitovich, P., Klose, J., Zöllner, S., Heissig, F., Giavalisco, P., et al. (2002). Intra- and interspecific variation in

primate gene expression patterns. Science, 296, 340–343.

ENCODE Project Consortium. (2012). An integrated encyclopedia of DNA elements in the human genome. Nature, 489, 57–74.

Endendijk, J. J., Groeneveld, M. G., Bakermans-Kranenburg, M. J., & Mesman, J. (2016). Gender-differentiated parenting revisited: Meta-analysis reveals very few differences in parental control of boys and girls. PLoS One, 11(7), e0159193. Retrieved from https://doi.org/10.1371/journal.pone.0159193

Eng, M. Y., Luczak, S. E., & Wall, T. L. (2007). ALDH2, ADH1B, and ADH1C genotypes in Asians: A literature review. Alcohol Research and Health, 30, 22–27.

Engel, A. K., König, P., Kreiter, A. K., & Singer, W. (1991). Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. Science, 252, 1177–1179.

Engel, A. K., Kreiter, A. K., König, P., & Singer, W. (1991). Synchronization of oscillatory neuronal responses between striate and extrastriate visual cortical areas of the cat. Proceedings of the National Academy of Sciences, 88, 6048–6052.

Engel, S. M., Villanger, G. D., Nethery, R. C., Thomsen, C., Sakhi, A. K., Drover, S. S. M., et al. (2018). Prenatal phthalates, maternal thyroid function, and risk of attention-deficit hyperactivity disorder in the Norwegian Mother and Child Cohort. Environmental Health Perspectives, 6(5). Retrieved from https://ehp.niehs.nih.gov/doi/10.1289/ehp2358

Enoch, M.-A. (2006). Genetic and environmental influences on the development of alcoholism: Resilience vs. risk. Annals of the New York Academy of Sciences, 1094, 193–201.

Enriori, P. J., Evans, A. E., Sinnayah, P., Jobst, E. E., Tonelli-Lemos, L., Billes, S. K., et al. (2007). Diet-induced obesity causes severe but reversible leptin resistance in arcuate melanocortin neurons. Cell Metabolism, 5, 181–194.

Eppig, C., Fincher, C. L., & Thornhill, R. (2010). Parasite prevalence and the worldwide distribution of cognitive ability. Proceedings of the Royal Society B. Retrieved from http://rspb.royalsocietypublishing.org/content/early/2010/06/29/rspb.2010.0973.full.pdf+html

Epstein, R. H. (2010, April 7). Raiding the refrigerator but still asleep. New York Times. Retrieved from https://www.nytimes.com/2010/04/07/health/07eating.html

Ercan-Sencicek, A. G., Stillman, A. A., Ghosh, A. K., Bilguvar, K., O'Roak, B. J., Mason, C. E., et al. (2010). l-Histidine decarboxylase and Tourette's syndrome. New England Journal of Medicine, 362, 1901–1908.

Erhardt, A., Akula, N., Schumacher, J., Czamara, D., Karbalai, N., Muller-Myhsok B, et al. (2012). Replication and meta-analysis of TMEM132D gene variants in panic disorder. Translational Psychiatry, 2, 156.

Erickson, K. I., Colcombe, S. J., Wadhwa, R., Bherer, L., Peterson, M. S., Scalf, P. E., et al. (2007). Training-induced plasticity in older adults: Effects of training on hemispheric asymmetry. Neurobiology of Aging, 28, 272–283.

Ernst, M., Zametkin, A. J., Matochik, J. A., Jons, P. H., & Cohen, R. M. (1998). DOPA decarboxylase activity in attention-deficit/hyperactivity disorder adults: A [fluorine-18]fluorodopa positron emission tomographic study. Journal of Neuroscience, 18, 5901–5907.

Ernulf, K. E., Innala, S. M., & Whitam, F. L. (1989). Biological explanation, psychological explanation, and tolerance of homosexuals: A cross-national analysis of beliefs and attitudes. Psychological Reports, 65, 1003–1010.

Ersche, K. D., Jones, P. S., Williams, G. B., Robbins, T. W., & Bullmore, E. T. (2012). Cocaine dependence: A fast-track for brain ageing? Molecular Psychiatry, 18, 134–135.

Ersche, K. D., Jones, P. S., Williams, G. B., Turton, A. J., Robbins, T. W., & Bullmore, E. T. (2012). Abnormal brain structure implicated in stimulant drug addiction. Science, 335, 601–604.

Ethier, C., Oby, E. R., Bauman, M. J., & Miller, L. E. (2012). Restoration of grasp following paralysis through brain-controlled stimulation of muscles. Nature, 485, 368–371.

Etkin, A., & Wager, T. D. (2007). Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. American Journal of Psychiatry, 164, 1476–1488.

Evans, S. M., Haney, M., & Foltin, R. W. (2002). The effects of smoked cocaine during the follicular and luteal phases of the menstrual cycle in women. Psychopharmacology (Berlin), 159, 397–406.

Evarts, E. V. (1979, March). Brain mechanisms of movement. Scientific American, 241, 164–179.

Faedda, G. L., Tondo, L., Teicher, M. H., Baldessarini, R. J., Gelbard, H. A., & Floris, G. F. (1993). Seasonal mood disorders: Patterns of seasonal recurrence in mania and depression. Archives of General Psychiatry, 50, 17–23.

Fahle, M., & Daum, I. (1997). Visual learning and memory as functions of age. Neuropsychologia, 35, 1583–1589.

Faigel, H. C., Szuajderman, S., Tishby, O., Turel, M., & Pinus, U. (1995). Attention-deficit disorder during adolescence: A review. Journal of Adolescent Health, 16, 174–184.

Falk, D. (2009). New information about Albert Einstein's brain. Frontiers in Evolutionary Neuroscience, 1, 1–6.

Falkner, A. L., & Lin, D. (2014). Recent advances in understanding the role of the hypothalamic circuit during aggression. Frontiers in Systems Neuroscience, 8, Article 168. doi:10.3389/fnsys.2014.00168

Falzi, G., Perrone, P., & Vignolo, L. A. (1982). Right-left asymmetry in anterior speech region. Archives of Neurology, 39, 239–240.

Fambrough, D. M., Drachman, D. B., & Satyamurti, S. (1973). Neuromuscular junction in myasthenia gravis: Decreased acetylcholine receptors. Science, 182, 293–295.

Fancher, R. E. (1979). Pioneers of psychology. New York, NY: W. W. Norton.

Fanelli, D. (2009). How many scientists fabricate and falsify research? A systematic review and meta-analysis of survey data. PloS ONE. doi:10.1371/journal.pone.0005738

Fanning, J. R., Keedy, S., Berman, M. E., Lee, R., & Coccaro, E. F. (2017). Neural correlates of aggressive behavior in real time: A review of fMRI studies of laboratory reactive aggression. Current Behavioral Neuroscience Reports, 4, 138–150.

Farina, D., Vujaklija, I., Sartori, M., Kapelner, T., Negro, F., Jiang, N., et al. (2017). Man/machine interface based on the discharge timings of spinal motor neurons after targeted muscle reinnervation. Nature Biomedical Engineering, 1, 0025. doi:10.1038/s41551-016-0025

Farooqi, I. S., Keogh, J. M., Yeo, G. S. H., Lank, E. J., Cheetham, T., & O'Rahilly, S. (2003). Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. New England Journal of Medicine, 348, 1085–1095.

Farooqi, I. S., Matarese, G., Lord, G. M., Keogh, J. M., Lawrence, E., Agwu, C., et al. (2002). Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. Journal of Clinical Investigation, 110, 1093–1103.

Farrer, C., Franck, N., Georgieff, N., Frith, C. D., Decety, J., & Jeannerod, M. (2003). Modulating the experience of agency. NeuroImage, 18, 324–333.

Farrer, C., Frey, S. H., Van Horn, J. D., Tunik, E., Turk, D., Inati, S., & Grafton, S. T. (2008). The angular gyrus computes action awareness representations. Cerebral Cortex, 18, 254–261.

Farrer, C., & Frith, C. D. (2002). Experiencing oneself vs another person as being the cause of an action: The neural correlates of the experience of agency. NeuroImage, 15, 596–603.

Farris, H. E., & Ryan, M. J. (2011). Relative comparisons of call parameters enable auditory grouping in frogs. Nature Communications, 2, 410.

Fasano, A., Daniele, A., & Albanese, A. (2012). Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. Lancet, 11, 429–442.

Fatemi, S. H., Earle, J. A., & McMenomy, T. (2000). Reduction in Reelin immunoreactivity in hippocampus of subjects with schizophrenia, bipolar disorder and major depression. Molecular Psychiatry, 5, 654–663.

Faul, M., Xu, L., Wald, M. M., & Coronado, V. G. (2010). Traumatic brain injury in the United States. Washington, DC: Centers for Disease Control and Prevention. Retrieved from https://www.cdc.gov/traumaticbraininjury/pdf/blue_book.pdf

Fava, M., Freeman, M. P., Flynn, M., Judge, H., Hoeppner, B. B., Cusin, C., et al. (2018). Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (RTD). Molecular Psychiatry, 25, 1592–1603. doi:10.1038/s41380-018-0256-5

Fawzy, F. I., Fawzy, N. W., Hyun, C. S., Elashoff, R., Guthrie, D., Fahey, J. L., et al. (1993). Malignant melanoma: Effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival 6 years later. Archives of General Psychiatry, 50, 681–689.

Federal financial conflict of interest rules and biomedical research: A legal overview. (2014, August 22). EveryCRSReport.com. Retrieved from https://www.everycrsreport.com/reports/R43693.html

Feinberg, T. E. (2001). Altered egos: How the brain creates the self. New York, NY: Oxford University Press.

Feinstein, J. S., Adolphs, R., Damasio, A., & Tranel, D. (2011). The human amygdala and the induction and experience of fear. Current Biology, 21, 34–38.

Feinstein, J. S., Buzza, C., Hurlemann, R., Follmer, R. I., Dahdalch, N. S., & Coryell, W. H. (2013). Fear and panic in humans with

bilateral amygdala damage. Nature Neuroscience, 16, 270–272.

Feng, L., Chong, M.-S., Lim, W.-S., Gao, Q., Nyunt, M. S. Z., Lee, T.-S., et al. (2016). Tea consumption reduces the incidence of neurocognitive disorders: Findings from the Singapore longitudinal aging study. Journal of Nutrition, Health & Aging, 20, 1002–1009.

Fenker, D. B., Frey, J. U., Schuetze, H., & Heipertz, D. (2008). Novel scenes improve recollection and recall of words. Journal of Cognitive Neuroscience, 20(7), 1250–1265.

Fenselau, H., Campbell, J. N., Verstegen, A. M., Madara, J. C., Xu, J., Shah, B. P., et al. (2017). A rapidly acting glutamatergic ARC/PVH satiety circuit postsynaptically regulated by α-MSH. Nature Neuroscience, 20, 42–51.

Fergusson, D., Doucette, S., Glass, K. C., Shapiro, S., Healy, D., Hebert, P., et al. (2005). Association between suicide attempts and selective serotonin reuptake inhibitors: Systematic review of randomised controlled trials. British Medical Journal, 330, 396–402.

Fernández, G., Effern, A., Grunwald, T., Pezer, N., Lehnertz, K., Dümpelmann, M., et al. (1999). Real-time tracking of memory formation in the human rhinal cortex and the hippocampus. Science, 285, 1582–1585.

Fernández, R., Esteva, I., Gómez-Gil, E., Rumbo, T., Almaraz, M. C., Roda, E., et al. (2014). Association study of ERβ, AR, and CYP19A1 genes and MtF transsexualism. Journal of Sexual Medicine, 11(12), 2986–2994.

Fernàndez-Castillo, N., & Cormand, B. (2016). Aggressive behavior in humans: Genes and pathways identified through association studies. American Journal of Medical Genetics Part B, 171B, 676–696.

Fernández-Real, J. M., Ferri, M. J., Vendrell, J., & Ricart, W. (2007). Burden of infection and fat mass in healthy middle-aged men. Obesity, 15, 245–252.

Ferrarelli, F., Sarasso, S., Guller, Y., Riedner, B. A., Peterson, M. J., Bellesi, M., et al. (2012). Reduced natural oscillatory frequency of frontal thalamocortical circuits in schizophrenia. Archives of General Psychiatry, 69, 766–774.

Ferrari, P. F., Gallese, V., Rizzolatti, G., & Fogassi, L. (2003). Mirror neurons responding to the observation of ingestive and communicative mouth actions in the monkey ventral premotor cortex. European Journal of Neuroscience, 17, 1703–1714.

Fertuck, H. C., & Salpeter, M. M. (1974). Localization of acetylcholine receptor by 1251-labeled alpha-bungarotoxin binding at mouse motor endplates. Proceedings of the National Academy of Sciences, 71, 1376–1378.

Fibiger, H. C., LePiane, F. G., Jakubovic, A., & Phillips, A. G. (1987). The role of dopamine in intracranial self-stimulation of the ventral tegmental area. Journal of Neuroscience, 7, 3888–3896.

Field, A. E., Coakley, E. H., Must, A., Spadano, J. L., Laird, N., Dietz, W. H., et al. (2001). Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Archives of Internal Medicine, 161, 1581–1586.

Fiez, J. (1996). Cerebellar contributions to cognition. Neuron, 16, 13–15.

Filiano, A. J., Xu, Y., Tustison, N. J., Marsh, R. L., Baker, W., Smirnov, I., et al. (2016). Unexpected role of interferon-γ in regulating neuronal connectivity and social behavior. Nature, 535, 425–429.

Fink, D. J., Wechuck, J., Mata, M., Glorioso, J. C., Goss, J., Krisky, D., & Wolfe, D. (2011). Gene therapy for pain: Results of a phase I clinical trial. Annals of Neurology, 70, 207–212.

Fink, G., Pfaff, D., & Levine, J. (2012). Handbook of neuroendocrinology. San Francisco, CA: Elsevier.

Fink, G. R., Markowitsch, H. J., Reinkemeier, M., Bruckbauer, T., Kessler, J., & Heiss, W.-D. (1998). Cerebral representation of one's own past: Neural networks involved in autobiographical memory. Journal of Neuroscience, 16, 4275–4282.

Finn, E. S., Shen, X., Holahan, J. M., Scheinost, D., Lacadie, C., Papademetris, X., et al. (2014). Disruption of functional networks in dyslexia: A whole-brain, data-driven analysis of connectivity. Biological Psychiatry, 76, 397–404.

Fiorino, D. F., Coury, A., & Phillips, A. G. (1997). Dynamic changes in nucleus accumbens dopamine efflux during the Coolidge effect in male rats. Journal of Neuroscience, 17, 4849–4855.

Fischer, T. Z., & Waxman, S. G. (2010). Familial pain syndromes from mutations of the Nav 1.7 sodium channel. Annals of the New York Academy of Sciences, 1184, 196–207.

Fiske, D. W., & Maddi, S. R. (1961). A conceptual framework. In D. W. Fiske & S. R. Maddi (Eds.), Functions of varied experience (pp. 11–56). Homewood, IL: Dorsey Press.

Flanagin, V. L., Schörnich, S., Schranner, M., Hummel, N., Wallmeier, L., Wahlberg, M., et al. (2017). Human exploration of enclosed spaces through echolocation. Journal of Neuroscience, 37(6), 1614–1627. doi:10.1523/JNEUROSCI.1566-12.2016w

Fleming, R., Baum, A., Gisriel, M. M., & Gatchel, R. J. (1982). Mediating influences of social support on stress at Three Mile Island. Journal of Human Stress, 8, 14–22.

Flor, H. (2008). Maladaptive plasticity, memory for pain and phantom limb pain: Review and suggestions for new therapies. Expert Review of Neurotherapeutics, 8, 809–818.

Flor, H., Braun, C., Elbert, T., & Birbaumer, N. (1997). Extensive reorganization of primary somatosensory cortex in chronic back pain patients. Neuroscience Letters, 224, 5–8.

Flor, H., Denke, C., Schaefer, M., & Grüsser, S. (2001). Effect of sensory discrimination training on cortical reorganisation and phantom limb pain. Lancet, 357, 1763–1764.

Flor, H., Diers, M., Christmann, C., & Koeppe, C. (2006). Mirror illusions of phantom hand movements: Brain activity mapped by fMRI. NeuroImage, 31, S159.

Flores, A. (2016). How many adults identify as transgender in the United States? Los Angeles, CA: Williams Institute, UCLA School of Law. Retrieved from http://williamsinstitute.law.ucla.edu/wp-content/uploads/How-Many-Adults-Identify-as-Transgender-in-the-United-States.pdf

Floresco, S. B., & Ghods-sharifi, S. (2007). Amygdala-prefrontal cortical circuitry regulates effort-based decision making. Cerebral Cortex, 17, 251–260.

Floresco, S. B., Montes, D. R., Maric, M. T. T., & van Holstein, M. (2018). Differential contributions of nucleus accumbens subregions to cue-guided risk/reward decision making and implementation of conditional rules. Journal of Neuroscience, 38, 1901–1914.

Floud, S., Simpson, R. F., Balkwill, A., Brown, A., Goodill, A., Gallacher, J., et al. (2020). Body mass index, diet, physical inactivity, and the incidence of dementia in 1 million UK women. Neurology, 94, e123–e132. Retrieved from https://n.neurology.org/content/94/2/e123

Flynn, J. R. (1987). Massive IQ gains in 14 nations: What IQ tests really measure. Psychological Bulletin, 101, 171–191.

Flynn, J. R., te Nijenhuis, J., & Metzen, D. (2014). The g beyond Spearman's g: Flynn's paradoxes resolved using four exploratory meta-analyses. Intelligence, 44, 1–10.

Foeli, J., Bekrater-Bodmann, R., Diers, M., & Flor, H. (2013). Mirror therapy for phantom limb pain: Brain changes and the role of body representation. European Journal of Pain, 18, 729–739.

Foerde, K., Steinglass, J. E., Shohamy, D., & Walsh, B. T. (2015). Neural mechanisms supporting maladaptive food choices in anorexia nervosa. Nature Neuroscience, 18, 1571–1573.

Ford, J. M., Mathalon, D. H., Whitfield, S., Faustman, W. O., & Roth, W. T. (2002). Reduced communication between frontal and temporal lobes during talking in schizophrenia. Biological Psychiatry, 51, 485–492.

Foreman, M., Hare, L., York, K., Balakrishnan, K., Sanchez, F. J., Harte, F., et al. (2019). Genetic link between gender dysphoria and sex hormone signalling. Journal of Clinical Endocrinology and Metabolism, 104, 390–396.

Foster, R. G., & Roenneberg, T. (2008). Human responses to the geophysical daily, annual, and lunar cycles. Current Biology, 18, PR784–PR794.

Fotopoulou, A., Solms, M., & Turnbull, O. (2004). Wishful reality distortions in confabulation: A case report. Neuropsychologia, 47, 727–744.

Fournier, J. C., DeRubeis, R. J., Hollon, S. D., Dimidjian, S., Amsterdam, J. D., Shelton, R. C., & Fawcett, J. (2010). Antidepressant drug effects and depression severity. Journal of the American Medical Association, 303, 47–53.

Fouts, R. S., Fouts, D. S., & Schoenfeld, D. (1984). Sign language conversational interactions between chimpanzees. Sign Language Studies, 42, 1–12.

Foverskov, E., Mortensen, E. L., Holm, A., Pedersen, J. L. M., Osler, M., & Lund, R. (2017). Socioeconomic position across the life course and cognitive ability later in life: the importance of considering early cognitive ability. Journal of Aging and Health, 31, 947–966.

Fowler, C. D., & Kenny, P. J. (2014). Nicotine aversion: Neurobiological mechanisms and relevance to tobacco dependence vulnerability. Neuropharmacology, 76 (Part B), 533–544.

Fowler, C. D., Liu, Y., & Wang, Z. (2007). Estrogen and adult neurogenesis in the amygdala and hypothalamus. Brain Research Reviews, 57, 342–351.

Fowler, J. S., Logan, J., Wang, G.-J., Volkow, N. D., Telang, F., Zhu, W., et al. (2003). Low monoamine oxidase B levels in peripheral organs in smokers. Proceedings of the National Academy of Sciences, 100, 11600–11605.

Fowler, J. S., Volkow, N. D., Wang, G.-J., Pappas, N., Logan, J., MacGregor, R., et al. (1996). Inhibition of monoamine oxidase B in the brains of smokers. Nature, 379, 733–736.

Fowler, R. (1986, May). Howard Hughes: A psychological autopsy. Psychology Today, 22–33.

Fowles, D. C. (1992). Schizophrenia: Diathesis-stress revisited. Annual Review of Psychology, 43, 303–336.

Fox, J. W., Lamperti, E. D., Eksioglu, Y. Z., Hong, S. E., Feng, Y., Graham, D. A., et al. (1998). Mutations in *filamin 1* prevent migration of cerebral cortical neurons in human periventricular heterotopia. Neuron, 21, 1315–1325.

Fox, M. J. (2002). Lucky man: A memoir. New York, NY: Hyperion.

Fraller, D. B. (2013). State of the science: Use of biomarkers and imaging in diagnosis and management of Alzheimer disease. Journal of Neuroscience Nursing, 45, 63–70.

Francis, H. W., Koch, M. E., Wyatt, J. R., & Niparko, J. K. (1999). Trends in educational placement and cost-benefit considerations in children with cochlear implants. Archives of Otolaryngology: Head and Neck Surgery, 125, 499–505.

Frank, G. K., Bailer, U. F., Henry, S. E., Drevets, W., Meltzer, C. C., Price, J. C., et al. (2005). Increased dopamine D2/D3 receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [11C]Raclopride. Biological Psychiatry, 58, P908–P912.

Frank, G. K. W., DeGuzman, M. C., Shott, M. E., Laudenslager, M. L., Rossi, B., & Pryor, T. (2018). Association of brain reward learning response with harm avoidance, weight gain, and hypothalamic effective connectivity in adolescent anorexia nervosa. JAMA Psychiatry, 75, 1071–1080.

Frank, G. K. W., Shott, M. E., Riederer, J., & Pryor, T. L. (2016). Altered structural and effective connectivity in anorexia and bulimia nervosa in circuits that regulate energy and reward homeostasis. Translational Psychiatry, 6, e932. doi:10.1038/tp.2016.199

Frankland, P. W., O'Brien, C., Ohno, M., Kirkwood, A., & Silva, A. J. (2001). α-CaMKII-dependent plasticity in the cortex is required for permanent memory. Nature, 411, 309–313.

Fratiglioni, L., & Wang, H. X. (2000). Smoking and Parkinson's and Alzheimer's disease: Review of the epidemiological studies. Behavioral Brain Research, 113, 117–120.

Frayling, T. M., Timson, N. J., Weedon, M. N., Zeggini, E., Freathy, R. M., Lindgren, C., et al. (2007). A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. Science, 316, 889–894.

Freed, C. R., Greene, P. E., Breeze, R. E., Tsai, W.-Y., DuMouchel, W., Kao, R., et al. (2001). Transplantation of embryonic dopamine neurons for severe Parkinson's disease. New England Journal of Medicine, 344, 710–719.

Freed, W. J., de Medinaceli, L., & Wyatt, R. J. (1985). Promoting functional plasticity in the damaged nervous system. Science, 227, 1544–1552.

Freedman, M. S., Lucas, R. J., Soni, B., von Schantz, M., Muñoz, M., David-Gray, Z., et al. (1999). Regulation of mammalian circadian behavior by non-rod, non-cone ocular photoreceptors. Science, 284, 502–504.

Freer, R., Sormanni, P., Vecchi, G., Ciryam, P., Dobson, C. M., & Vendruscolo, M. (2016). A protein homeostasis signature in healthy brains recapitulates tissue vulnerability to Alzheimer's

disease. Science Advances, 2(8), e1600947. doi:10.1126/sciadv.1600947

French, S. J., & Cecil, J. E. (2001). Oral, gastric, and intenstinal influences on human feeding. Physiology and Behavior, 74, 729–734.

French roast. (1996, July). Harper's Magazine, 293, 28–30.

Frequency Therapeutics. (2019). Our sensorineural hearing loss program. Retrieved from https://www.frequencytx.com/pipeline-programs/hearing-program

Freund, P., Schmidlin, E., Wannier, T., Bloch, J., Mir, A., Schwab, M. E., et al. (2006). Nogo-A-specific antibody treatment enhances sprouting and functional recovery after cervical lesion in adult primates. Nature Medicine, 12, 790–792.

Freund, P., Wannier, T., Schmidlin, E., Bloch, J., Mir, A., Schwab, M. E., et al. (2007). Anti-Nogo-A antibody treatment enhances sprouting of corticospinal axons rostral to a unilateral cervical spinal cord lesion in adult Macaque monkey. Journal of Comparative Neurology, 502, 644–659.

Fried, P., Watkinson, B., James, D., & Gray, R. (2002). Current and former marijuana use: Preliminary findings of a longitudinal study of effects on IQ in young adults. Canadian Medical Association Journal, 166, 887–891.

Fried, P. A. (1995). The Ottawa Prenatal Prospective Study (OPPS): Methodological issues and findings—It's easy to throw the baby out with the bath water. Life Sciences, 56, 23–24.

Friederici, A. D. (2006). The neural basis of language development and its impairment. Neuron, 52, 941–952.

Friedman, J. H. (2013). Pimavanserin for the treatment of Parkinson's disease psychosis. Expert Opinion on Pharmacotherapy, 14(14), 1969–1975.

Friedrich-Schiller-Universität Jena. (2010, August 9). Prosthesis with information at its fingertips: Hand prosthesis that eases phantom pain. Science Daily. Retrieved from https://www.sciencedaily.com/releases/2010/08/100806125508.htm

Frieling, H., Römer, K. D., Scholz, S., Mittelbach, F., Wilhelm, J., De Zwaan, M., et al. (2010). Epigenetic dysregulation of dopaminergic genes in eating disorders. International Journal of Eating Disorders, 43, 577–583.

Friend, L., Weed, J., Sandoval, P., Nufer, T., Ostlund, I., & Edwards, J. G. (2017). CB1-dependent long-term depression in ventral tegmental area GABA neurons: A novel target for marijuana. Journal of Neuroscience, 37, 10943–10954.

Frings, L., Wagner, K., Unterrainer, J., Spreer, J., Halsband, U., & Schulze-Bonhage, A. (2006). Gender-related differences in lateralization of hippocampal activation and cognitive strategy. Neuroreport, 17, 417–421.

Frisén, L., Nordenström, A., Falhammar, H., Filipsson, H., Holmdahl, G., Janson, P. O., et al. (2009). Gender role behavior, sexuality, and psychosocial adaptation in women with congenital adrenal hyperplasia due to *CYP21A2* deficiency. Journal of Clinical Endocrinology and Metabolism, 94, 3432–3439.

Friston, K. J. (2009). Modalities, modes, and models in functional neuroimaging. Science, 326, 399–403.

Frith, U. (1993, June). Autism. Scientific American, 268, 108–114.

Frith, U., Morton, J., & Leslie, A. M. (1991). The cognitive basis of a biological disorder: Autism. Trends in Neuroscience, 14, 433–438.

Fritsch, G., & Hitzig, E. (1870). Über die elektrische Erregbarkeit des Grosshirns [Concerning the electrical stimulability of the cerebrum]. Archiv für Anatomie Physiologie und Wissenschaftliche Medicin, 37, 300–332.

Fritschy, J.-M., & Grzanna, R. (1992). Degeneration of rat locus coeruleus neurons is not accompanied by an irreversible loss of ascending projections. Annals of the New York Academy of Sciences, 648, 275–278.

Fritz, H.-C., Wittfield, K., Schmidt, C. O., Domin, M., Grabe, H. J., Hegenscheid, K., et al. (2014). Current smoking and reduced gray matter volume—A voxel-based morphometry study. Neuropsychopharmacology, 39(11). doi:10.1038/npp.2014.112

Fujii, M., Maesawa, S., Ishiai, S., Iwami, K., Futamura, M., & Saito, K. (2016). Neural basis of language: An overview of an evolving model. Neurologia Medico-Chirurgica, 56, 379–386.

Fullerton, D. T., Getto, C. J., Swift, W. J., & Carlson, I. H. (1985). Sugar, opioids and binge eating. Brain Research Bulletin, 14, 673–680.

Fuster, J. M. (1989). The prefrontal cortex: Anatomy, physiology, and neuropsychology of the frontal lobe (2nd ed.). New York, NY: Raven Press.

Fuster, J. M., & Jervey, J. P. (1981). Inferotemporal neurons distinguish and retain behaviorally relevant features of visual stimuli. Science, 212, 952–955.

Gabrieli, J. D. E. (1998). Cognitive neuroscience of human memory. Annual Review of Psychology, 49, 87–115.

Gackenbach, J., & Bosveld, J. (1989). Control your dreams. New York, NY: Harper & Row.

Gage, F. H. (2000). Mammalian neural stem cells. Science, 287, 1433–1438.

Gaderman, A. M., Alonso, J., Valagut, G., Zaslavsky, A. M., & Kessler, R. C. (2012). Comorbidity and disease burden in the national comorbidity survey replication (NCS-R). Depression & Anxiety, 29, 797–806.

Gaillard, R., Dehaene, S., Adam, C., Clémenceau, S., Hasboun, D., Baulac, M., et al. (2009). Converging intracranial markers of conscious access. PLoS Biology, 7, e1000061. Retrieved from https://www.plosbiology.org/article/info:doi/10.1371/journal.pbio.1000061

Gaillard, R., Naccache, L., Pinel, P., Clémenceau, S., Volle, E., Hasboun, D., et al. (2006). Direct intracranial, fMRI, and lesion evidence for the causal role of left inferotemporal cortex in reading. Neuron, 50, 191–204.

Gale, J. T., Amirnovin, R., Roberts, D. W., Williams, Z. M., Blaha, C. D., & Eskandar, E. N. (2013). Electrical stimulation-evoked dopamine release in the primate striatum. Stereotactic and Functional Neurosurgery, 91, 355–363.

Gallese, V., & Goldman, A. (1998). Mirror neurons and the simulation theory of mind-reading. Trends in Cognitive Sciences, 2, 493–501.

Gallotto, S., Sack, A. T., Schuhmann, T., & de Graaf, T. A. (2017). Oscillatory correlates of visual consciousness. Frontiers in

Psychology, 8, 1147. Retrieved from https://doi.org/10.3389/fpsyg.2017.01147

Gallup. (2019). Gay and lesbian rights. Retrieved from https://news.gallup.com/poll/1651/gay-lesbian-rights.aspx

Gallup, G. G. (1983). Toward a comparative psychology of mind. In R. L. Mellgren (Ed.), Animal cognition and behavior (pp. 473–510). New York, NY: North-Holland.

Gallup, G., Jr., & Povinelli, D. J. (1998, Winter). Can animals empathize? Scientific American Presents, 66–75.

Ganna, A., Verweij, K. J. H., Nivard, M. G., Maier, R., Wedow, R., Busch, A. S., et al. (2019). Large-scale GWAS reveals insights into the genetic architecture of same-sex sexual behavior. Science, 365(6456), eaat7693. Retrieved from https://science.sciencemag.org/content/365/6456/eaat7693

Gannon, P. J., Holloway, R. L., Broadfield, D. C., & Braun, A. R. (1998). Asymmetry of chimpanzee planum temporale: Human-like pattern of Wernicke's brain language area homolog. Science, 279, 220–222.

Ganzel, B. L., Kim, P., Glover, G. H., & Temple, E. (2008). Resilience after 9/11: Multimodal neuroimaging evidence for stress-related change in the healthy adult brain. NeuroImage, 40, 788–795.

Gao, Q., & Horvath, T. L. (2007). Neurobiology of feeding and energy expenditure. Annual Review of Neuroscience, 30, 367–398.

Garb, J. L., & Stunkard, A. J. (1974). Taste aversions in man. American Journal of Psychiatry, 131, 1204–1207.

Garcia, J., & Koelling, R. A. (1966). Relation of cue to consequence in avoidance learning. Psychonomic Science, 4, 123–124.

Garcia-Falgueras, A., & Swaab, D. F. (2008). A sex difference in the hypothalamic uncinate nucleus: Relationship to gender identity. Brain, 131, 3132–3146.

Gardner, E. P., & Johnson, K. O. (2013a). The somatosensory system: Receptors and central pathways. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), Principles of neural science (5th ed., pp. 475–497). New York, NY: McGraw-Hill.

Gardner, E. P., & Johnson, K. O. (2013b). Touch. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), Principles of neural science (5th ed., pp. 498–529). New York, NY: McGraw-Hill.

Gardner, G., & Halweil, B. (2000). Overfed and underfed: The global epidemic of malnutrition. Worldwatch Institute. Retrieved from https://www.worldwatch.org/system/files/EWP150.pdf

Gardner, H. (1975). The shattered mind. New York, NY: Alfred A. Knopf.

Garelick, T. & Swann, J. (2014). Testosterone regulates the density of dendritic spines in the male preoptic area. Hormones and Behavior, 65, 249–253.

Garrigan, P., Ratliff, C. P., Klein J. M., Sterling, P., Brainard, D. H., & Balasubramanian, V. (2010). Design of a trichromatic cone array. PLoS Computational Biology, 6, e1000677. Retrieved from http://www.ploscompbiol.org/article/info%3Adoi%2F10.1371%2Fjournal.pcbi.1000677

Gartrell, N. K. (1982). Hormones and homosexuality. In W. Paul, J. D. Weinrich, J. C. Gonsiorek, & M. E. Hotvedt (Eds.), Homosexuality: Social, psychological, and biological issues (pp. 169–182). Beverly Hills, CA: Sage.

Gasparini, F., Di Paolo, T., & Gomez-Mancilla, B. (2013). Metabotropic glutamate receptors for Parkinson's disease therapy. Parkinson's Disease, Article ID 196028. Retrieved from http://www.hindawi.com/journals/pd/2013/196028

Gatchel, R. J. (1996). Psychological disorders and chronic pain: Cause-and-effect relationships. In R. J. Gatchel & D. C. Turk (Eds.), Psychological approaches to pain management: A practitioner's handbook (pp. 33–52). New York, NY: Guilford Press.

Gates, G. J. (2011). How many people are lesbian, gay, bisexual, and transgender? Los Angeles, CA: Williams Institute, UCLA School of Law. Retrieved from https://williamsinstitute.law.ucla.edu/publications/how-many-people-lgbt

Gauthier, I., Skudlarski, P., Gore, J. C., & Anderson, A. W. (2000). Expertise for cars and birds recruits brain areas involved in face recognition. Nature Neuroscience, 3, 191–197.

Gauthier, I., Tarr, M. J., Anderson, A. W., Skudlarski, P., & Gore, J. C. (1999). Activation of the middle fusiform "face area" increases with expertise in recognizing novel objects. Nature Neuroscience, 2, 568–573.

Gawin, F. H. (1991). Cocaine addiction: Psychology and neurophysiology. Science, 251, 1580–1586.

Gayán, J., & Olson, R. K. (2001). Genetic and environmental influences on orthographic and phonological skills in children with

reading disabilities. Developmental Neuropsychology, 20, 483–507.

Gazdic, M., Volarevic, V., Harrell, C. R., Fellabaum, C., Jovicic, N., Arsenijevic, N., Strojkovic, M. (2018). Stem cells therapy for spinal cord injury. International Journal of Molecular Sciences, 1039. doi:10.3390/ijms19041039

Gazzaniga, M. S. (1967, August). The split brain in man. Scientific American, 217, 24–29.

Gazzaniga, M. S. (1970). The bisected brain. New York, NY: Appleton-Century-Crofts.

Gazzaniga, M. S. (2002). The split brain revisited. Scientific American, 12(1), 27–31.

Gazzaniga, M. S., Ivry, R. B., & Mangun, G. R. (1998). Cognitive neuroscience: The biology of the mind. New York, NY: Norton.

Gazzola, V., Aziz-Zadeh, L., & Keysers, C. (2006). Empathy and the somatotopic auditory mirror system in humans. Current Biology, 16, 1824–1829.

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet, 392, 1789–1858.

Gebhardt, C. A., Naeser, M. A., & Butters, N. (1984). Computerized measures of CT scans of alcoholics: Thalamic region related to memory. Alcohol, 1, 133–140.

Gefter, A. (2008, October 22). Creationists declare war over the brain. New Scientist, 46–47.

Gegenfurtner, K. R., & Kiper, D. C. (2003). Color vision. Annual Review of Neuroscience, 26, 181–206.

Geiss, L. S., Wang, J., Cheng, Y. J., Thompson, T. J., Barker, L., Li, Y., et al. (2014). Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980–2012. Journal of the American Medical Association, 312, 1218–1226.

Gelosa, G., & Brooks, D. J. (2012). The prognostic value of amyloid imaging. European Journal of Nuclear Medicine and Molecular Imaging, 39, 1207–1219.

Gene therapy for APOE4 homozygote of Alzheimer's disease. (2019, November 20). ClinicalTrials.gov. Retrieved from https://clinicaltrials.gov/ct2/show/NCT03634007

Geniole, S. N., Procyshyn, T. L., Marley, N., Ortiz, T. L., Bird, B. M., Marcellus, A. L., et al. (2019). Using a psychopharmacogenetic approach to identify the pathways through which—and the people for whom—testosterone promotes aggression. Psychological Science, 30, 481–494.

Genoux, D., Haditsch, U., Knobloch, M., Michalon, A., Storm, D., & Mansuy, I. M. (2002). Protein phosphatase 1 is a molecular constraint on learning and memory. Nature, 418, 970–975.

Gentner, T. Q., Fenn, K. M., Margoliash, D., & Nusbaum, H. C. (2006). Recursive syntactic pattern learning by songbirds. Nature, 440(7088), 1204–1207.

Georgopoulos, A. P., Taira, M., & Lukashin, A. (1993). Cognitive neurophysiology of the motor cortex. Science, 260, 47–52.

Gerloff, C., Bushara, K., Sailer, A., Wasserman, E. M., Chen, R., Matsuoka, T., et al. (2006). Multimodal imaging of brain reorganization in motor areas of the contralesional hemisphere of well recovered patients after capsular stroke. Brain, 129, 791–808.

German education minister quits over PhD plagiarism. (2013, February 9). The Guardian. Retrieved from http://www.theguardian.com/world/2013/feb/09/german-education-minister-quits-phd-plagiarism

Gershon, E. S., Bunney, W. E., Leckman, J. F., Van Eerdewegh, M., & DeBauche, B. A. (1976). The inheritance of affective disorders: A review of data and of hypotheses. Behavior Genetics, 6, 227–261.

Gershoni, M., & Pietrokovski, S. (2017). The landscape of sex-differential transciptome and its consequent selection in human adults. BMC Biology, 15(7). doi:10.1186/s12915-017-0352-z

Gertler, P., Heckman, J., Pinto, R., Zanolini, A., Vermeersch, C., Walker, S., et al. (2014). Labor market returns to an early childhood stimulation intervention in Jamaica. Science, 344, 998–1001.

Geschwind, N. (1970). The organization of language and the brain. Science, 170, 940–944.

Geschwind, N. (1972, April). Language and the brain. Scientific American, 226(4), 76–83.

Geschwind, N. (1979, September). Specializations of the human brain. Scientific American, 241, 180–199.

Geschwind, N., & Levitsky, W. (1968). Human brain: Left-right asymmetries in temporal speech region. Science, 161, 186–187.

Geyer, M. A., & Vollenweider, F. X. (2008). Serotonin research: contributions to understanding psychosis. Trends in Pharmacological Sciences, 29, 445–453.

Ghilardi, J. R., Röhrich, H., Lindsay, T. H., Sevcik, M. A., Schwei, M. J., Kubota, K., et al. (2005). Selective blockade of the capsaicin receptor TRPV1 attenuates bone cancer pain. Journal of Neuroscience, 25, 3126–3131.

Ghorayshi, A. (2017, July 27). A landmark lawsuit about an intersex baby's genital surgery just settled for $440,000. BuzzFeed News. Retrieved from https://www.buzzfeednews.com/article/azeenghorayshi/intersex-surgery-lawsuit-settles

Ghosh, A., & Sinha, A. K. (2007). A second Charak festival from Delhi. Anthropologist, 9, 289–294.

Gibbons, J. (Ed.) (2013). Global study on homicide. Vienna, Austria: United Nations Office on Drugs and Crime. Retrieved from http://www.unodc.org/documents/gsh/pdfs/2014_GLOBAL_HOMICIDE_BOOK_web.pdf

Gibbons, R. D., Brown, C. H., Hur, K., Marcus, S. M., Bhaumik, D. K., Erkens, J. A., et al. (2007). Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. American Journal of Psychiatry, 164, 1356–1363.

Giedke, H., & Schwärzler, F. (2002). Therapeutic use of sleep deprivation in depression. Sleep Medicine Reviews, 6(5), 361–377.

Gilad, Y., Wiebe, V., Przeworski, M., Lancet, D., & Pääbo, S. (2004). Loss of olfactory receptor genes coincides with the acquisition of full trichromatic vision in primates. Public Library of Science Biology, 2, 120–125.

Gilaie-Dolan, S., Tymula, A., Cooper, N., Kable, J. W., Glimcher, P. W., & Levy, I. (2014). Neuroanatomy predicts individual risk attitudes. Journal of Neuroscience, 34, 12394–12401.

Gilbert, J., & Man, H.-Y. (2017). Fundamental elements in autism: From neurogenesis and neurite growth to synaptic plasticity. Frontiers in Cellular Neuroscience, 11, 359. Retrieved from https://www.frontiersin.org/articles/10.3389/fncel.2017.00359/full

Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P., et al. (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nature Neuroscience, 5, 1242–1247.

Giles, D. E., Biggs, M. M., Rush, A. J., & Roffwarg, H. P. (1988). Risk factors in families of unipolar depression: I. Psychiatric illness and reduced REM latency. Journal of Affective Disorders, 14, 51–59.

Gilliland, F. D., Li, Y. F., & Peters, J. M. (2001). Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. American Journal of Respiratory Critical Care Medicine, 163, 429–436.

Gipson, C. D., Kupchik, Y. M., & Kalivas, P. W. (2014). Rapid, transient synaptic plasticity in addiction. Neuropharmacology, 76, 276–286.

Gitlin, M. J., & Altshuler, L. L. (1997). Unanswered questions, unknown future for one of our oldest medications. Archives of General Psychiatry, 54, 21–23.

Giza, B. K., Scott, T. R., & Vanderweele, D. A. (1992). Administration of satiety factors and gustatory responsiveness in the nucleus tractus solitarius of the rat. Brain Research Bulletin, 28, 637–639.

Gizewski, E. R., Krause, E., Schlamann, M., Happich, F., Ladd, M. E., Forsting, M., et al. (2009). Specific cerebral activation due to visual erotic stimuli in male-to-female transsexuals compared with male and female controls: An fMRI study. Journal of Sexual Medicine, 6, 440–448.

Gizowski, C., & Bourque, C. W. (2018). Hypothalamic neurons controlling water homeostasis: It's about time. Current Opinion in Physiology, 5, 45–50.

Gladue, B. A., Beatty, W. W., Larson, J., & Staton, R. D. (1990). Sexual orientation and spatial ability in men and women. Psychobiology, 18, 101–108.

Gläscher, J., Rudrauf, D., Colom, R., Paul, L. K., Tranel, D., Damasio, H., et al. (2010). Distributed neural system for general intelligence revealed by lesion mapping. Proceedings of the National Academy of Sciences, 107, 4705–4709.

Glaser, R., Rice, J., Sheridan, J., Fertel, R., Stout, J., Speicher, C., et al. (1987). Stress-related immune suppression: Health implications. Brain, Behavior, and Immunity, 1, 7–20.

Glasson, B. I., Duda, J. E., Murray, I. V. J., Chen, Q., Souza, J. M., Hurtig, H. I., et al. (2000). Oxidative damage linked to neuro degeneration by selective a-synuclein nitration in synucleinopathy lesions. Science, 290, 985–989.

Glees, P. (1980). Functional cerebral reorganization following hemispherectomy in man and after small experimental lesions in primates. In P. Bach-y-Rita (Ed.), Recovery of function: Theoretical

considerations for brain injury rehabilitation (pp. 106–125). Berne, Switzerland: Hans Huber.

Glenn, A. L., & Raine, R. (2014). Neurocriminology: Implications for the punishment, prediction and prevention of criminal behavior. Nature Reviews Neuroscience, 15, 54–63. doi:10.1038/nrn3640

Glezer, L. S., Jiang, X., & Riesenhuber, M. (2009). Evidence for highly selective neuronal tuning to whole words in the “visual word form area.” Neuron, 62, 199–204.

Goate, A., Chartier-Harlin, M. C., Mullan, M., Brown, J., Crawford, F., Fidani, L., et al. (1991). Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer’s disease. Nature, 349, 704–706.

Godfrey, K. M., Sheppard, A., Gluckman, P. D., Lillycrop, K. A., Burdge, G. C., et al. (2011). Epigenetic gene promoter methylation at birth is associated with child’s later adiposity. Diabetes, 60, 1528–1534.

Gold, M. S. (1997). Cocaine (and crack): Clinical aspects. In J. H. Lowinson, P. Ruiz, R. B. Millman, & J. G. Langrod (Eds.), Substance abuse: A comprehensive textbook (pp. 181–199). Baltimore, MD: Williams & Wilkins.

Gold, P. W., Goodwin, F. K., & Chrousos, G. P. (1988). Clinical and biochemical manifestations of depression: Relation to the neurobiology of stress. New England Journal of Medicine, 319, 348–353.

Goldberg, M., & Rosenberg, H. (1987). New muscle relaxants in outpatient anesthesiology. Dental Clinics of North America, 31, 117–129.

Goldberg, M. E., Walker, M. F., & Hudspeth, A. J. (2013). The vestibular system. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), Principles of neural science (5th ed., pp. 917–934). New York, NY: McGraw-Hill.

Goldman, N., Chen, M., Fujita, T., Xu, Q., Peng, W., Liu, W., et al. (2010). Adenosine A1 receptors mediate local anti-nociceptive effects of acupunctures. Nature Neuroscience, 13 [electronic version]. Retrieved from www.nature.com/neuro/journal/vaop/ncurrent/full/nn.2562.html

Goldman-Rakic, P. S., Bates, J. F., & Chafee, M. V. (1992). The prefrontal cortex and internally generated motor acts. Current Opinion in Neurobiology, 2, 830–835.

Goldstein, E. B. (1999). Sensation and perception (5th ed.). Pacific Grove, CA: Brooks-Cole.

Goldstein, J. M., Scidman, L. J., Horton, N. J., Makris, N., Kennedy, D. N., Caviness, V. S., Jr., et al. (2001). Normal sexual dimorphism of the adult human brain assessed by *in vivo* magnetic resonance imaging. Cerebral Cortex, 11, 490–497.

Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. American Journal of Psychiatry, 10, 1642–1652.

Gomez-Tortosa, E., Martin, E. M., Gaviria, M., Charbel, F., & Auman, J. I. (1995). Selective deficit of one language in a bilingual patient following surgery in the left perisylvian area. Brain and Language, 48, 320–325.

Gong, Y., Chang, L., Viola, K. L., Lacor, P. N., Lambert, M. P., Finch, C. E., et al. (2003). Alzheimer's disease-affected brain: Presence of oligomeric Ab ligands (ADDLs) suggests a molecular basis for

reversible memory loss. Proceedings of the National Academy of Sciences, 100, 10417–10422.

González, G. F., & Karipidis, I. I., & Tijms, J. (2018). Dyslexia as a neurodevelopmental disorder and what makes it different from a chess disorder. Brain Sciences, 8, 189. doi:10.3390/brainsci8100189. Retrieved from https://www.mdpi.com/2076-3425/8/10/189

González-Maeso, J., Ang, R. L., Yen, T., Chan, P., Weisstaub, N. V., López-Giménez, J. F., et al. (2008). Identification of a serotonin/glutamate receptor complex implicated in psychosis. Nature, 452, 93–99.

Gooch, C. L., Pracht, E., & Borenstein, A. R. (2017). The burden of neurological disease in the United States: A summary report and call to action. Annals of Neurology, 81, 479–484.

Goodell, E. W., & Studdert-Kennedy, M. (1993). Acoustic evidence for the development of gestural coordination in the speech of 2-year-olds: A longitudinal study. Journal of Speech and Hearing Research, 36, 707–727.

Goodman, D. C., Bogdasarian, R. S., & Horel, J. A. (1973). Axonal sprouting of ipsilateral optic tract following opposite eye removal. Brain, Behavior, and Evolution, 8, 27–50.

Goodwin, D. W. (1986). Heredity and alcoholism. Annals of Behavioral Medicine, 8, 3–6.

Gooley, J. J., Chamberlain, K., Smith, K. A., Khalsa, S. B. S., Rajaratnam, S. M. W., Van Reen, E., et al. (2011). Exposure to room light before bedtime suppresses melatonin onset and shortens melatonin duration in humans. Journal of Clinical Endocrinology & Metabolism, 96, E463–E472. doi:10.1210/jc.2010-2098.

Gorey, C. (2019, June 11). Lethal neurotoxin offers unexpected hope for opioid-free painkiller. Silicon Republic. Retrieved from https://www.siliconrepublic.com/innovation/pufferfish-neurotoxin-opioid-free-painkiller

Gorski, R. A. (1974). The neuroendocrine regulation of sexual behavior. In G. Newton & A. H. Riesen (Eds.), Advances in psychobiology (Vol. 2, pp. 1–58). New York, NY: Wiley.

Gorzalka, B. B., Mendelson, S. D., & Watson, N. V. (1990). Serotonin receptor subtypes and sexual behavior. Annals of the New York Academy of Sciences, 600, 435–446.

Gottesman, I. I. (1991). Schizophrenia genesis: The origins of madness. New York, NY: Freeman.

Gottesman, I. I., & Bertelsen, A. (1989). Confirming unexpressed genotypes for schizophrenia. Archives of General Psychiatry, 46, 867–872.

Gottesman, I. I., McGuffin, P., & Farmer, A. E. (1987). Clinical genetics as clues to the “real genetics” of schizophrenia (a decade of modest gains while playing for time). Schizophrenia Bulletin, 13, 12–47.

Gougoux, F., Zatorre, R. J., Lassonde, M., Voss, P., & Lepore, F. (2005). A functional neuroimaging study of sound localization: Visual cortex activity predicts performance in early-blind individuals. Public Library of Science Biology, 3, 1–9.

Gould, E., & Gross, C. G. (2002). Neurogenesis in adult mammals: Some progress and problems. Journal of Neuroscience, 22, 619–623.

Gouras, P. (1968). Identification of cone mechanisms in monkey ganglion cells. Journal of Physiology, 199, 533–547.

Graham, J. M., & Desjardins, C. (1980). Classical conditioning: Induction of luteinizing hormone and testosterone secretion in anticipation of sexual activity. Science, 210(4473), 1039–1041.

Graham, K. E., Hobaiter, C., Ounsley, J., Furuichi, T., & Byrne, R. W. (2018). Bonobo and chimpanzee gestures overlap extensively in meaning. PLoS Biology, 16(2), e2004825. Retrieved from https://doi.org/10.1371/journal.pbio.2004825

Grant, B. F., Chou, S. P., Goldstein, R. B., Huang, B., Stinson, F. S., Saha, T. D., et al. (2008). Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: Results from the Wave 2 national epidemiologic survey on alcohol and related conditions. Journal of Clinical Psychiatry, 69, 533–545.

Grant, B. F., Stinson, F. S., Dawson, D. A., Chou, P., Dufour, M. C., Compton, W., et al. (2004). Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders. Archives of General Psychiatry, 61, 807–816.

Grant, B. F., Stinson, F. S., Dawson, D. A., Chou, S. P., Ruan, W. J., & Pickering, R. P. (2004). Co-occurrence of 12-month alcohol and drug use disorders and personality disorders in the United States. Archives of General Psychiatry, 61, 361–368.

Grant, S., London, E. D., Newlin, D. B., Villemagne, V. L., Liu, X., Contoreggi, C., et al. (1996). Activation of memory circuits during cue-elicited cocaine craving. Proceedings of the National Academy of Sciences, 93, 12040–12045.

Gray, J. (1992). Men are from Mars, women are from Venus: A practical guide for improving communication and getting what you want in your relationships. New York, NY: HarperCollins.

Gray, K., & Wegner, D. M. (2008). The sting of intentional pain. Psychological Science, 19, 1260–1262.

Graybiel, A. M. (1998). The basal ganglia and chunking of action repertoires. Neurobiology of Learning and Memory, 70, 119–136.

Graybiel, A. M., & Rauch, S. L. (2000). Toward a neurobiology of obsessive-compulsive disorder. Neuron, 28, 343–347.

Graziano, M. S. A., Cooke, D. F., & Taylor, C. S. R. (2000). Coding the location of the arm by sight. Science, 290, 1782–1786.

Graziano, M. S. A., Hu, X. T., & Gross, C. G. (1997). Visuospatial properties of ventral premotor cortex. Journal of Neurophysiology, 77, 2268–2292.

Graziano, M. S. A., Taylor, C. S. R., & Moore, T. (2002). Complex movements evoked by microstimulation of precentral cortex. Neuron, 34, 841–851.

Graziano, M. S. A., Yap, G. S., & Gross, C. G. (1994). Coding of visual space by premotor neurons. Science, 266, 1054–1057.

Green, E. L. (2019, November 6). Flint's children suffer in class after years of drinking the lead-poisoned water. New York Times. Retrieved from https://www.nytimes.com/2019/11/06/us/politics/flint-michigan-schools.html

Greenamyre, J. T., & Hastings, T. G. (2004). Parkinson's: Divergent causes, convergent mechanisms. Science, 304, 1120–1122.

Greene, P. E., & Fahn, S. (2002). Status of fetal tissue transplantation for the treatment of advanced Parkinson disease.

Neurosurgery Focus, 13, 1–4.

Greenfeld, L. A., & Henneberg, M. A. (2001). Victim and offender self-reports of alcohol involvement in crime. Alcohol Research and Health, 25, 20–31.

Greenough, W. T. (1975). Experiential modification of the developing brain. American Scientist, 63, 37–46.

Greer, S. M., Goldstein, A. N., & Walker, M. P. (2013). The impact of sleep deprivation on food desire in the human brain. Nature Communications, 4, 2259. Retrieved from http://www.nature.com/ncomms/2013/130806/ncomms3259/full/ncomms3259.html#access

Gregory, S. G., Barlow, K. F., McLay, K. E., Kaul, R., Swarbreck, D., Dunham, A., et al. (2006). The DNA sequence and biological annotation of human chromosome 1. Nature, 441, 315–321.

Gressens, P., Lammens, M., Picard, J. J., & Evrard, P. (1992). Ethanol-induced disturbances of gliogenesis and neurogenesis in the developing murine brain: An *in vitro* and an *in vivo* immunohistochemical and ultrastructural study. Alcohol and Alcoholism, 27, 219–226.

Grèzes, J., Armony, J. L., Rowe, J., & Passingham, R. E. (2003). Activations related to “mirror” and “canonical” neurones in the human brain: An fMRI study. NeuroImage, 18, 928–937.

Griffith, J. D., Cavanaugh, J., Held, J., & Oates, J. A. (1972). Dextroamphetamine: Evaluation of psychomimetic properties in man. Archives of General Psychiatry, 26, 97–100.

Griffiths, K. R., Grieve, S. M., Kohn, M. R., Clarke, S., Williams, L. M., & Korgaonkar, M. S. (2016). Altered gray matter organization

in children and adolescents with ADHD: A structural covariance connectome study. Translational Psychiatry, 6, e947. doi:10.1038/tp2016.219

Grilo, C. M., & Pogue-Geile, M. F. (1991). The nature of environmental influences on weight and obesity: A behavior genetic analysis. Psychological Bulletin, 110, 520–537.

Grimm, D. (2014, March 12). Animal rights extremists increasingly targeting individuals. Science. Retrieved from http://news.sciencemag.org/policy/2014/03/animal-rights-extremists-increasingly-targeting-individuals

Grimm, D. (2018a, November 2). Record number of monkeys being used in U.S. research. Science. Retrieved from https://www.sciencemag.org/news/2018/11/record-number-monkeys-being-used-us-research

Grimm, D. (2018b, March 21). U.S. chimp retirement gains momentum, as famed pair enters sanctuary. Science. Retrieved from https://www.sciencemag.org/news/2018/03/us-chimp-retirement-gains-momentum-famed-pair-enters-sanctuary

Grindlinger, H. M., & Ramsay, E. (1991). Compulsive feather-picking in birds. Archives of General Psychiatry, 48, 857.

Gross, C. G., Rocha-Miranda, C. E., & Bender, D. B. (1972). Visual properties of neurons in inferotemporal cortex of the macaque. Journal of Neurophysiology, 35, 96–111.

Grothe, B., & Pecka, M. (2014). The natural history of sound localization in mammals—A story of neuronal inhibition. Frontiers in Neural Circuits, 8, 116. Retrieved from https://www.frontiersin.org/articles/10.3389/fncir.2014.00116/full

Grotzinger, A. D., Mann, F. D., Patterson, M. W., Tackett, J. L., Tucker-Drob, E. M., & Harden, K. P. (2018). Hair and salivary testosterone, hair cortisol, and externalizing behaviors in adolescents. Psychological Science. Retrieved from https://journals.sagepub.com/doi/full/10.1177/0956797617742981

Grubb, M. A., Tymula, A., Gilaie-Dolan, S., Glimcher, P. W., & Levy, I. (2016). Neuroanatomy accounts for age-related changes in risk preferences. Nature Communications. doi:10.1038/ncomms13822

Gruenewald, D. A., & Matsumoto, A. M. (2003). Testosterone supplementation therapy for older men: Potential benefits and risks. Journal of the American Geriatrics Society, 51, 101–115.

Grueter, T. (2007, August/September). Forgetting faces. Scientific American Mind, 69–73.

Grupe, D. W., Hushek, B. A., Davis, K., Schoen, A. J., Wielgosz, J., Nitschke, J. B., & Davidson, R. J. (2019). Elevated perceived threat is associated with reduced hippocampal volume in combat veterans. Scientific Reports, 9 (1), 14888.

Grüter, T., Grüter, M., & Carbon, C.-C. (2008). Neural and genetic foundations of face recognition and prosopagnosia. Journal of Neuropsychology, 2, 79–97.

Gu, X., Hof, P. R., Friston, K. J., & Fan, J. (2013). Anterior insular cortex and emotional awareness. Journal of Comparative Neurology, 52, 3371–3388. doi:10.1038/s41598-019-51533-x

Guerreiro, M., Castro-Caldas, A., & Martins, I. P. (1995). Aphasia following right hemisphere lesion in a woman with left hemisphere injury in childhood. Brain and Language, 49, 280–288.

Guidotti, A., Auta, J., Davis, J. M., Gerevini, V. D., Dwivedi, Y., Grayson, D. R., et al. (2000). Decrease in Reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder. Archives of General Psychiatry, 57, 1061–1069.

Gulsuner, S., Stein, D. J., Susser, E. S., Sibeko, G., Pretorius, A., Walsh, T., et al. (2020). Genetics of schizophrenia in the South African Xhosa. Science, 367, 569–573.

Gurd, J. M., & Marshall, J. C. (1992). Drawing upon the mind's eye. Nature, 359, 590–591.

Gusella, J. F., Wexler, N. S., Conneally, P. M., Naylor, S. L., Anderson, M. A., Tanzi, R. E., et al. (1983). A polymorphic DNA marker genetically linked to Huntington's disease. Nature, 306, 234–238.

Gustafson, D., Lissner, L., Bengtsson, C., Björkelund, C., & Skoog, I. (2004). A 24-year follow-up of body mass index and cerebral atrophy. Neurology, 63, 1876–1881.

Gustavson, C. R., Garcia, J., Hankins, W. G., & Rusiniak, K. W. (1974). Coyote predation control by aversive conditioning. Science, 184, 581–583.

Gustavson, C. R., Jowsey, J. R., & Milligan, D. N. (1982). A 3-year evaluation of taste aversion coyote control in Saskatchewan. Journal of Range Management, 35, 57–59.

Gustavson, C. R., Kelly, D. J., Sweeney, M., & Garcia, J. (1976). Prey lithium aversions I: Coyotes and wolves. Behavioral Biology, 17, 61–72.

Gustavson, D. E., Miyake, A., Hewitt, J. K., & Friedman, N. P. (2014). Genetic relations among procrastination, impulsivity, and goal-

management ability: Implications for the evolutionary origin of procrastination. Psychological Science, 25, 1178–1188.

Guzowski, J. F., Knierim, J. J., & Moser, E. I. (2004). Ensemble dynamics of hippocampal regions of CA3 and CA1. Neuron, 44, 581–584.

György, B., Sage, C., Indzhykulian, A. A., Scheffer, D. I., Brisson, A. R., Tan, S., et al. (2017). Rescue of hearing by gene delivery to inner-ear hair cells using exosome-associated AAV. Molecular Therapy, 25, 379–391.

Haaxma, C., Bloem, B. R., Borm, G. F., Oyen, W. J. G., Leenders, K. L., Eshuis, S., et al. (2007). Gender differences in Parkinson's disease. Journal of Neurology and Neurosurgical Psychiatry, 78, 819–824.

Habib, M. (2000). The neurological basis of developmental dyslexia: An overview and working hypothesis. Brain, 123, 2373–2399.

Haedt-Matt, A. A., & Keel, P. K. (2011). Revisiting the affect regulation model of binge eating: A meta-analysis of studies using ecological momentary assessment. Psychological Bulletin, 137, 660–681.

Hagoort, P. (2016). MUC (Memory, unification, control): A model on the neurobiology of language beyond single word processing. In G. Hickok & S. L. Small (Eds.), Neurobiology of language. London, UK: Academic Press. Retrieved from https://doi.org/10.1016/B978-0-12-407794-2.00028-6

Haier, R. J., Chueh, D., Touchette, P., Lott, I., Buchsbaum, M. S., MacMillan, D., et al. (1995). Brain size and cerebral glucose metabolic rate in nonspecific mental retardation and Down syndrome. Intelligence, 20, 191–210.

Haier, R. J., Siegel, B., Tang, C., Abel, L., & Buchsbaum, M. S. (1992). Intelligence and changes in regional cerebral glucose metabolic rate following learning. Intelligence, 16, 415–426.

Haijma, S. V., Van Haren, N., Cahn, W., Kooschijn, C. M. P., Hulshoff Pol, H. E.., & Kahn, R. S. (2012). Brain volumes in schizophrenia: A meta-analysis in over 18000 subjects. Schizophrenia Bulletin, 39, 1129–1138.

Halaas, J. L., Gajiwala, K. S., Maffei, M., Cohen, S. L., Chait, B. T., Rabinowitz, D., et al. (1995). Weight-reducing effects of the plasma protein encoded by the obese gene. Science, 269, 543–546.

Hales, C. M., Carroll, M. D., Fryar, C. D., & Ogden, C. L. (2017). Prevalence of obesity among adults and youth: United States, 2015–2016. National Center for Health Statistics, Data Brief No. 288. Retrieved from https://www.cdc.gov/nchs/data/databriefs/db288.pdf

Hale, L., Kirschen, G. W., LeBourgeois, M. K., Gradisar, M., Garrison, M. M., Montgomery-Downs, H., et al. (2018). Youth screen media habits and sleep: Sleep-friendly screen-behavior recommendations for clinicians, educators, and parents. Child and Adolescent Psychiatry Clinics of North America, 27, 229–245.

Haliloglu, G., Becker, K., Temucin, C., Talim, B., Küçükşahin, N., Pergande, M., et al. (2016). Recessive PIEZO2 stop mutation causes distal arthrogryposis with distal muscle weakness, scoliosis and proprioception defects. Journal of Human Genetics, 62, 497–501.

Hall, M. H., Taylor, G., Salisbury, D. F., & Levy, D. L. (2010, April 2). Sensory gating event-related potentials and oscillations in schizophrenia patients and their unaffected relatives. Schizophrenia Bulletin (advanced online publication). doi:10.1093/schbul/sbq027

Halley, A. C., Boretsky, M., Puts, D. A., & Shriver, M. (2016). Self-reported sexual behavioral intersets and polymorphisms in the dopamine receptor D4 (DRD4) exon III VNTR in heterosexual young adults. Archives of Sexual Behavior, 48, 2091–2100.

Hallmayer, J., Faraco, J., Lin, L., Hesselson, S., Winkelmann, J., Kawashima, M., et al. (2009). Narcolepsy is strongly associated with the T-cell receptor alpha locus. Nature Genetics, 41, 708–711.

Hallock, R. M., & Di Lorenzo, P. M. (2006). Temporal coding in the gustatory system. Neuroscience and Biobehavioral Reviews, 30(8), 1145–1160.

Hamann, S. B., Ely, T. D., Grafton, S. T., & Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. Nature Neuroscience, 2, 289–293.

Hamblin, J. (2019, May 14). Why the government pays billions to people who claim injury by vaccines. The Atlantic. Retrieved from https://www.theatlantic.com/health/archive/2019/05/vaccine-safety-program/589354

Hamer, D. H. (1999). Genetics and male sexual orientation. Science, 285, 801–802.

Hamer, D. H., Hu, S., Magnuson, V. L., Hu, N., & Pattatucci, A. M. L. (1993). A linkage between DNA markers on the X chromosome and male sexual orientation. Science, 261, 321–327.

Hamza, T. H., Chen, H., Hill-Burns, E. M., Rhodes, S. L., Montimurro, J., Kay, D. M., et al. (2011). Genome-wide gene-environment study identifies glutamate receptor gene GRIN2A as a Parkinson's disease modifier gene via interaction with coffee. PLOS Genetics, 7(8), e1002237.

Han, F., Lin, L., Warby, S. C., Faraco, J., Li, J., Dong, S. X., An, P., et al. (2011). Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. Annals of Neurology, 70, 410–417.

Han, L., Ma, C., Liu, Q., Weng, H.-J., Cui, Y., Tang, Z., et al. (2012). A subpopulation of nociceptors specifically linked to itch. Nature Neuroscience, 16, 174–182.

Han, X., Chen, M., Wang, F., Windrem, M., Wang, B., Shanz, S., et al. (2013). Forebrain engraftment by human glial progenitor cells enhances synaptic plasticity and learning in adult mice. Cell Stem Cell, 12, 342–353.

Handelsman, D. J., Hirschberg, A., & Bermon, S. (2018). Circulating testosterone as the hormonal basis of sex diffeences in athletic performance. Endocrine Reviews, 39, 803–829.

Hänig, D. (1901). Zur psychophysik des geschmackssinnes. Philosophische Studien, 17, 576–623.

Hanlon, E. M., & Bir, C. A. (2012). Real-time head acceleration measurement in girls' youth soccer. Medicine & Science in Sports & Exercise, 44, 1102–1108.

Hannula-Jouppi, K., Kaminen-Ahola, N., Taipale, M., Eklund, R., Nopola-Hemmi, J., Kääriäinen, H., & Kere, J. (2005). The axon guidance receptor gene ROBO1 is a candidate gene for developmental dyslexia. PLoS Genetics, 1(4), 467–474.

Haqq, C. M., King, C.-Y., Ukiyama, E., Falsafi, S., Haqq, T. N., Donahoe, P. K., et al. (1994). Molecular basis of mammalian sexual determination: Activation of Müllerian inhibiting substance gene expression by SRY. Science, 266, 1494–1500.

Harada, C. N., Love, M. C. N., & Triebel, K. (2013). Normal cognitive aging. Clinical Geriatric Medicine, 29, 737–752.

Hare, L., Bernard, P., Sánchez, F. J., Baird, P. N., Vilain, E., Kennedy, T., & Harley, V. R. (2009). Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. Biological Psychiatry, 65, 93–96.

Hariri, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., et al. (2002). Serotonin transporter genetic variation and the response of the human amygdala. Science, 297, 400–403.

Harmon, L. D., & Julesz, B. (1973). Masking in visual recognition: Effects of two-dimensional filtered noise. Science, 180, 1194–1197.

Harrison, P. J., Colbourne, L., & Harrison, C. H. (2018). The neuropathology of bipolar disorder: Systematic review and meta-analysis. Molecular Psychiatry. Retrieved from https://doi.org/10.1038/s41380-018-0213-3

Harrison, P. J., Freemantle, N., & Geddes, J. R. (2003). Meta-analysis of brain weight in schizophrenia. Schizophrenia Research, 64, 25–34.

Hart, B. (1968). Role of prior experience on the effects of castration on sexual behavior of male dogs. Journal of Comparative and Physiological Psychology, 66, 719–725.

Hartig, H., & Geiger, A. W. (2018, October 8). About six-in-ten Americans support marijuana legalization. Washington, DC: Pew Research Center. Retrieved from https://www.pewresearch.org/fact-tank/2018/10/08/americans-support-marijuana-legalization

Hartman, L. (1995). Cats as possible obsessive-compulsive disorder and medication models. American Journal of Psychiatry, 152, 1236.

Harvard Medical School. (2017, August 21). 2007 national comorbidity survey (NCS). Retrieved from https://www.hcp.med.harvard.edu/ncs/index.php

Harvey, A. G., & Bryant, R. A. (2002). Acute stress disorder: A synthesis and critique. Psychological Bulletin, 128, 886–902.

Harvey, S. M. (1987). Female sexual behavior: Fluctuations during the menstrual cycle. Journal of Psychosomatic Research, 31, 101–110.

Hashikawa, K., Hashikawa, Y., Tremblay, R., Zhang, J., Feng, J. E., Sabol, A., et al. (2017). ESr1+ cells in the ventromedial hypothalamus control female aggression. Nature Neuroscience, 20, 1580–1590.

Hashimoto, M., Kato, S., Tanabe, Y., Katakura, M., Mamun, A. A., Ohno, M., et al. (2016). Beneficial effects of dietary docosahexaenoic acid intervention on cognitive function and mental health of the oldest elderly in Japanese care facilities and nursing homes. Geriatrics and Gerontology International, 17, 330–337. doi:10.1111/ggi.12691

Hassabis, D., Chu, C., Rees, G., Weiskopf, N., Molyneux, P. D., & Maguire, E. A. (2009). Decoding neuronal ensembles in the human hippocampus. Current Biology, 19, 546–554.

Hastings, M. H., Reddy, A. B., & Maywood, E. S. (2003). A clockwork web: Circadian timing in brain and periphery, in health and disease. Nature Reviews Neuroscience, 4, 649–661.

Hattar, S., Liao, H.-W., Takao, M., Berson, D. M., & Yau, K.-W. (2002). Melanopsin-containing retinal ganglion cells: Architecture, projections, and intrinsic photosensitivity. Science, 295, 1065–1070.

Hauglund, N. L., Pavan, C., & Nedergaard, M. (2020). Cleaning the sleeping brain—The potential restorative function of the glymphatic system. Current Opinion in Physiology, 15. Retrieved from https://www.sciencedirect.com/science/article/pii/S2468867319301609

Hauk, O., Johnsrude, I., & Pulvermüller, F. (2004). Somatotopic representation of action words in human motor and premotor cortex. Neuron, 41, 301–307.

Hauri, P. (1982). Current concepts: The sleep disorders. Kalamazoo, MI: Upjohn.

Hauser, M. D., MacNeilage, P., & Ware, M. (1996). Numerical representations in primates. Proceedings of the National Academy of Sciences, 93, 1514–1517.

Häusser, M., & Smith, S. L. (2007). Controlling neural circuits with light. Nature, 446, 617–619.

Hawass, Z. (2010). Ancestry and pathology in King Tutankhamun's family. Journal of the American Medical Association, 303, 638. doi:10.1001/jama.2010.121

Haworth, C. M. A., Wright, M. J., Luciano, M., Martin, N. G., de Geus, E. J. C., van Beijsterveld, C. E. M., et al. (2009). The heritability of general cognitive ability increases linearly from childhood to young adulthood. Molecular Psychiatry. Retrieved from

https://www.nature.com/mp/journal/vaop/ncurrent/abs/mp200955a.html

Haxby, J. V., Gobbini, M. I., Furey, M. L., Ishai, A., Schouten, J. L., & Pietrini, P. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science, 293, 2425–2430.

Hayes, K. J., & Hayes, C. (1953). Picture perception in a home-raised chimpanzee. Journal of Comparative and Physiological Psychology, 46, 470–474.

He, Z., Ferguson, S. A., Cui, L., Greenfield, L. J., & Paule, M. G. (2013). Development of the sexually dimorphic nucleus of the preoptic area and the influence of estrogen-like compounds. Neural Regeneration Research, 8, 2763–2774.

Heath, R. G. (1964). The role of pleasure in behavior. New York, NY: Harper & Row.

Hebb, D. O. (1940). The organization of behavior. New York, NY: Wiley-Interscience.

Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology, 80, 1778–1783.

Hedges, L. V., & Nowell, A. (1995). Sex differences in mental test scores, variability, and numbers of high-scoring individuals. Science, 269, 41–45.

Heim, N. (1981). Sexual behavior of castrated sex offenders. Archives of Sexual Behavior, 10, 11–19.

Heller, A. S., Johnstone, T., Light, S. N., Peterson, M. J., Kolden, G. G., Kalin, N. H., & Davidson, R. J. (2013). Relationships between changes in sustained fronto-striatal connectivity and positive affect in major depression resulting from antidepressant treatment. American Journal of Psychiatry, 170, 197–206.

Helmholtz, H. von. (1852). On the theory of compound colors. Philosophical Magazine, 4, 519–534.

Helmholtz, H. von. (1948). On the sensations of tone as a physiological basis for the theory of music (A. J. Ellis, Trans.). New York, NY: P. Smith. (Original work published 1863)

Helmuth, L. (2002). A generation gap in brain activity. Science, 296, 2131–2132.

Hendler, R. A., Ramchandani, V. A., Gilman, J., & Hommer, D. W. (2013). Stimulant and sedative effects of alcohol. Current Topics in Behavioral Neuroscience, 13, 489–509.

Heni, M., Kullmann, S., Ahlqvist, E., Wagner, R., Machicao, F., Staiger, H., et al. (2016). Interaction between the obesity-risk gene *FTO* and the dopamine D2 receptor gene *ANKK1/TaqIA* on insulin sensitivity. Diabetologia, 59, 2622–2631.

Hennenlotter, A., Dresel, C., Castrop, F., Ceballos Baumann, A. O., Wolschläger, A. M., & Haslinger, B. (2009). The link between facial feedback and neural activity within central circuitries of emotion: New insights from botulinum toxin-induced denervation of frown muscles. Cerebral Cortex, 19, 537–542.

Hennevin, E., Hars, B., Maho, C., & Bloch, V. (1995). Processing of learned information in paradoxical sleep: Relevance for memory. Behavioral Brain Research, 69, 125–135.

Herbeck, D. (2015, December 26). Woman's body acts as "brewery," so judge dismisses DWI. Buffalo News. Retrieved from http://www.buffalonews.com/city-region/police-courts/womans-body-acts-as-brewery-so-judge-dismisses-dwi-20151226

Herbert, T. B., Cohen, S., Marsland, A. L., Bachen, E. A., Rabin, B. S., Muldoon, M. F., et al. (1994). Cardiovascular reactivity and the course of immune response to an acute psychological stressor. Psychosomatic Medicine, 56, 337–344.

Herculano-Houzel, S. (2017). Numbers of neurons as biological correlates of cognitive capability. Current Opinion in Behavioral Sciences, 16, 1–7.

Hering, E. (1878). Zur lehre vom lichtsinne. Vienna, Austria: Gerold.

Heritch, A. J. (1990). Evidence for reduced and dysregulated turnover of dopamine in schizophrenia. Schizophrenia Bulletin, 16, 605–615.

Herkenham, M. A., & Pert, C. B. (1982). Light microscopic localization of brain opiate receptors: A general autoradiographic method which preserves tissue quality. Journal of Neuroscience, 2, 1129–1149.

Hermann, L. (1870). Eine erscheinung simultanen contrastes. Pflügers Archiv für die gesamte Physiologie, 3, 13–15.

Hernán, M. A., Zhang, S. M., Lipworth, L., Olek, M. J., & Ascherio, A. (2001). Multiple sclerosis and age at infection with common viruses. Epidemiology, 12, 301–306.

Heron, M. (2019). Deaths: Leading causes for 2017. National Vital Statistics Reports, 68(6). Retrieved from https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_06-508.pdf

Heron, M., Hoyert, D. L., Murphy, S. L., Xu, J., Kochanek, K. D., & Tejada-Vera, B. (2009). Deaths: Final data for 2006. National Vital Statistics Reports, 57(14). Retrieved from https://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_14.pdf

Hervey, G. R. (1952). The effects of lesions in the hypothalamus in parabiotic rats. Journal of Physiology, 145, 336–352.

Herzog, D. B., Dorer, D. J., Keel, P. K., Selwyn, S. E., Ekeblad, E. R., Flores, A. T., et al. (1999). Recovery and relapse in anorexia and bulimia nervosa: A 7.5-year follow-up study. Journal of the American Academy of Child and Adolescent Psychiatry, 38, 829–837.

Herzog, H. A. (1998). Understanding animal activism. In L. A. Hart (Ed.), Responsible conduct with animals in research (pp. 165–184). New York, NY: Oxford University Press.

Hesselbrock, V., Begleiter, H., Porjesz, B., O'Connor, S., & Bauer, L. (2001). P300 event-related potential amplitude as an endophenotype of alcoholism: Evidence from the collaborative study on the genetics of alcoholism. Journal of Biomedical Science, 8, 77–82.

Heston, L. L. (1970). The genetics of schizophrenic and schizoid disease. Science, 167, 249–256.

Hettema, J. M., Prescott, C. A., Myers, J. M., Neale, M. C., & Kendler, K. S. (2005). The structure of genetic and environmental risk factors for anxiety disorders in men and women. Archives of General Psychiatry, 62, 182–189.

Heywood, C. A., & Kentridge, R. W. (2003). Achromatopsia, color vision, and cortex. Neurological Clinics of North America, 21, 483–500.

Hickey, P., & Stacy, M. (2012). Adenosine A2A antagonists in Parkinson's disease: What's next? Current Neurology and Neuroscience Reports, 12, 376–385.

Hickok, G., Bellugi, U., & Klima, E. S. (1996). The neurobiology of sign language and its implications for the neural basis of language. Nature, 381, 699–702.

Hicks, B. M., Bernat, E., Malone, S. M., Iacono, W. G., Patrick, C. J., Krueger, R. F., et al. (2007). Genes mediate the association between P3 amplitude and externalizing disorders. Psychophysiology, 44, 98–105.

Higley, J. D., Mehlman, P. T., Poland, R. E., Taub, D. M., Vickers, J., Suomi, S. J., et al. (1996). CSF testosterone and 5-HIAA correlate with different types of aggressive behaviors. Biological Psychiatry, 40, 1067–1082.

Higuchi, S., Usui, A., Murasaki, M., Matsushita, S., Nishioka, N., Yoshino, A., et al. (2002). Plasma orexin-A is lower in patients with narcolepsy. Neuroscience Letters, 318, 61–64.

Hill, J. O., Schlundt, D. G., Sbrocco, T., Sharp, T., Pope-Cordle, J., Stetson, B., et al. (1989). Evaluation of an alternating-calorie diet with and without exercise in the treatment of obesity. American Journal of Nutrition, 50, 248–254.

Hill, J. O., Wyatt, H. R., Reed, G. W., & Peters, J. C. (2003). Obesity and the environment: Where do we go from here? Science, 299, 853–855.

Hill, N. T., Mowszowski, L., Naismith, S. L., Chadwick, V. L., Valenzuela, M., & Lampit, A. (2017). Computerized cognitive training in older adults with mild cognitive impairment or dementia: A systematic review and meta-analysis. American Journal of Psychiatry, 174, 329–340.

Hill, S. (1995). Neurobiological and clinical markers for a severe form of alcoholism in women. Alcohol Health and Research World, 19(3), 249–259.

Hill, S. Y., Muka, D., Steinhauer, S., & Locke, J. (1995). P300 amplitude decrements in children from families of alcoholic female probands. Biological Psychiatry, 38, 622–632.

Hillier, L. W., Coulson, A., & Murray, J. I. (2005). Genomics in C. elegans: So many genes, such a little worm. Genome Research, 15, 1651–1660.

Hines, M. (1982). Prenatal gonadal hormones and sex differences in human behavior. Psychological Bulletin, 92, 56–80.

Hines, P. J. (1997). Noto bene: Unconscious odors. Science, 278, 79.

Hines, T. (1998). Further on Einstein's brain. Experimental Neurology, 150, 343–344.

Hipolide, D. C., Moreira, K. M., Barlow, K. B., Wilson, A. A., Nobrega, J. N., & Tufik, S. (2005). Distinct effects of sleep deprivation on binding to norepinephrine and serotonin transporters in rat brain. Progress in Neuro-Psychopharmacology &Biological Psychiatry, 29, 297–303.

Hirayasu, Y., Sato, S.-I., Takahashi, H., Iida, S., Shuto, N., Yoshida, S., et al. (2016). A double-blind randomized study assessing safety and efficacy following one-year adjunctive treatment with pitopertin, a glycine reuptake inhibitor, in Japanese patients with schizophrenia. BMC Psychiatry, 16, e66.

Hirnstein, M., Hugdahl, K., & Hausmann, M. (2019). Cognitive sex differences and hemispheric asymmetry: A critical review of 40

years of research. Laterality: Asymmetries of Body, Brain and Cognition, 24, 204–252.

Hirsch, L. E., & Pringsheim, T. (2016). Aripiprazole for autism spectrum disorders (ASD). Cochrane Database of Systematic Reviews, (6), Article CD009043. Retrieved from https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009043.pub3/full

Ho, A. C., & Avery, R. L. (2019, May/June). Gene therapy trials for wet age-related macular degeneration. Retina Today. Retrieved from http://retinatoday.com/2019/06/gene-therapy-trials-for-wet-age-related-macular-degeneration

Hochberg, L. R., Bacher, D., Jarosiewicz, B., Masse, N. Y., Simeral, J. D., Vogel, J., et al. (2012). Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. Nature, 485, 372–377.

Hochberg, L. R., Serruya, M. D., Friehs, G. M., Muskand, J. A., Saleh, M., Caplan, A. H., et al. (2006). Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature, 442, 164–171.

Hochner, H., Friedlander, Y., Calderon-Margalit, R., Meiner, V., Sagy, Y., Avgil-Tsadok, M., et al. (2012). Associations of maternal prepregnancy body mass index and gestational weight gain with adult offspring cardiometabolic risk factors. Circulation, 125, 1381–1389.

Hoffman, P. L., & Tabakoff, B. (1993). Ethanol, sedative hypnotics and glutamate receptor function in brain and cultured cells. Alcohol and Alcoholism Supplement, 2, 345–351.

Hohmann, A. G., Suplita, R. L., Bolton, N. M., Neely, M. H., Fegley, D., Mangieri, R., et al. (2005). An endocannabinoid mechanism for

stress-induced analgesia. Nature, 435, 1108–1112.

Holden, C. (2004a). The origin of speech. Science, 303, 1316–1319.

Holden, C. (2004b). What's in a chimp's toolbox? Science NOW. Retrieved from https://sciencenow.sciencemag.org/cgi/content/full/2004/1007/2

Holloway, T., Moreno, J. L., Umali, A., Rayannavr, V., Hodes, G. E., Russo, S. J., & González-Maeso, J. (2013). Prenatal stress induces schizophrenia-like alterations of serotonin 2A and metabotropic glutamate 2 receptors in the adult offspring: Role of maternal immune system. Journal of Neuroscience, 33, 1088–1098.

Holstege, G., Georgiadis, J. R., Paans, A. M. J., Meiners, L. C., van der Graaf, F. H. C. E., & Reinders, A. A. T. S. (2003). Brain activation during human male ejaculation. Journal of Neuroscience, 23, 9185–9193.

Honea, R., Crow, T. J., Passingham, D., & MacKay, C. E. (2005). Regional deficits in brain volume in schizophrenia: A meta-analysis of voxel-based morphometry studies. American Journal of Psychiatry, 162, 2233–2245.

Hoogman, M., Bralten, J., Hibar, D. P., Mennes, M., Zwiers, M. P., Schweren, L. S., et al. (2017). Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: A cross-sectional mega-analysis. Lancet Psychiatry, 4, 310–319.

Hooks, B. M., & Chen, C. (2007). Critical periods in the visual system: Changing views for a model of experience-dependent plasticity. Neuron, 56, 312–326.

Hopkins, W. D., & Morris, R. D. (1993). Hemispheric priming as a technique in the study of lateralized cognitive processes in chimpanzees: Some recent findings. In H. L. Roitblat, L. M. Herman, & P. E. Nachtigall (Eds.), Language and communication: Comparative perspectives (pp. 293–309). Hillsdale, NJ: Lawrence Erlbaum.

Hopson, J. S. (1979). Scent signals: The silent language of sex. New York, NY: Morrow.

Horgan, J. (1999). The undiscovered mind. New York, NY: Free Press.

Horne, J. (1988). Why we sleep: The functions of sleep in humans and other mammals. New York, NY: Oxford University Press.

Horne, J. (1992). Human slow wave sleep: A review and appraisal of recent findings, with implications for sleep functions, and psychiatric illness. Experientia, 48, 941–954.

Horne, J. A., & Harley, L. J. (1989). Human SWS following selective head heating during wakefulness. In J. Horne (Ed.), Sleep ’88 (pp. 188–190). New York, NY: Gustav Fischer Verlag.

Horne, J. A., & Moore, V. J. (1985). Sleep EEG effects of exercise with and without additional body cooling. Electroencephalography and Clinical Neurophysiology, 60, 33–38.

Horner, P. J., & Gage, F. H. (2000). Regenerating the damaged central nervous system. Nature, 407, 963–970.

Horton, C., D’Zmura, M., & Srinivasan, R. (2013). Suppression of competing speech through entrainment of cortical oscillations. Journal of Neurophysiology, 109, 3082–3093.

Horvath, T. L., & Wikler, K. C. (1999). Aromatase in developing sensory systems of the rat brain. Journal of Neuroendocrinology, 11, 77–84.

Hoshi, E., Shima, K., & Tanji, J. (2000). Neuronal activity in the primate prefrontal cortex in the process of motor selection based on two behavioral rules. Journal of Neurophysiology, 83, 2355–2373.

Hoshi, E., & Tanji, J. (2000). Integration of target and body-part information in the premotor cortex when planning action. Nature, 408, 466–470.

Hough, C. M., Luks, T. L., Lai, K., Vigil, O., Guillory, S., Nongpiur, A., et al. (2016). Comparison of brain activation patterns during executive function tasks in hoarding disorder and non-hoarding OCD. Psychiatry Research: Neuroimaging, 255, 50–59.

Hough, G. E., Nelson, D. A., & Volman, S. F. (2000). Re-expression of songs deleted during vocal development in white-crowned sparrows, Zonotrichia leucophrys. Animal Behaviour, 60, 279–287.

Howell, M., & Schenck, C. H. (2020). Rapid eye movement sleep behavior disorder. UpToDate. Retrieved from https://www.uptodate.com/contents/rapid-eye-movement-sleep-behavior-disorder

Howes, O. D., & Nour, M. N. (2016). Dopamine and the aberrant salience hypothesis of schizophrenia. World Psychiatry, 15, 3–4.

Hser, Y.-I., Hoffman, V., Grella, C. E., & Anglin, M. D. (2001). A 33-year follow-up of narcotics addicts. Archives of General Psychiatry, 58, 503–508.

Hsiao, S. S., O'Shaughnessy, D. M., & Johnson, K. O. (1993). Effects of selective attention on spatial form processing in monkey primary and secondary somatosensory cortex. Journal of Neurophysiology, 70, 444–447.

Hu, S., Pattatucci, A. M., Patterson, C., Li, L., Fulker, D. W., Cherny, S. S., et al. (1995). Linkage between sexual orientation and chromosome Xq28 in males but not in females. Nature: Genetics, 11(3), 248–256.

Hu, V. W., Sarachana, T., Sherrard, R. M., & Kocher, K. M. (2015). Investigation of sex differences in the expression of *RORA* and its transcriptional targets in the brain as a potential contributor to the sex bias in autism. Molecular Autism, 6, 7. doi:10.1186/2040-2392-6-7

Huang, Y.-T., Maccani, J. Z. J., Hawley, N. L., Wing, R. R., Kelsey, K. T., & McCaffery, J. M. (2015). Epigenetic patterns in successful weight loss maintainers: A pilot study. International Journal of Obesity, 39, 865–868.

Hubbard, E. M., Arman, A. C., Ramachandran, V. S., & Boynton, G. M. (2005). Individual differences among grapheme-color synesthetes: Brain-behavior correlations. Neuron, 45, 975–985.

Hubel, D. H. (1982). Exploration of the primary visual cortex, 1955–78. Nature, 299, 515–524.

Hubel, D. H., & Wiesel, T. N. (1959). Receptive fields of single neurons in the cat's striate cortex. Journal of Physiology, 148, 574–591.

Hubel, D. H., & Wiesel, T. N. (1974). Sequence regularity and geometry of orientation columns in the monkey striate cortex. Journal of Comparative Neurology, 158, 267–294.

Huber, G., Gross, G., Schüttler, R., & Linz, M. (1980). Longitudinal studies of schizophrenic patients. Schizophrenia Bulletin, 6, 593–605.

Huberman, A. D. (2007). Mechanisms of eye-specific visual circuit development. Current Opinion in Neurobiology, 17, 73–80.

Hudson, J. L., Hiripi, E., Pope, H. G., Jr., & Kessler, R. C. (2007). The prevalence and correlates of eating disorders in the National Comorbidity Survey replication. Biological Psychiatry, 61, 348–358.

Hudspeth, A. J. (1989). How the ear's works work. Nature, 341, 397–404.

Hudspeth, A. J. (2008). Making an effort to listen: Mechanical amplification in the ear. Neuron, 59, 530–545.

Hudspeth, A. J. (2013). The inner ear. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), Principles of neural science (5th ed., pp. 654–681). New York, NY: McGraw-Hill.

Hull, C. L. (1951). Essentials of behavior. New Haven, CT: Yale University Press.

Hull, E. M., Muschamp, J. W., & Sato, S. (2004). Dopamine and serotonin: Influences on male sexual behavior. Physiology and Behavior, 83, 291–307.

Hull, J. T., Czeisler, C. A., & Lockley, S. W. (2018). Suppression of melatonin secretion in totally visually blind people by ocular exposure to white light: clinical characteristics. Ophthalmology, 125, 1160–1171.

Hulshoff Pol, H. E., Cohen-Kettenis, P. T., Van Haren, N. E. M., Peper, J. S., Brans, R. G. H., Cahn, W., et al. (2006). Changing your sex changes your brain: Influences of testosterone and estrogen on adult human brain structure. European Journal of Endocrinology, 155, S107–S114.

The Human Memory. (2019). Brain neurons & synapses. Retrieved from https://human-memory.net/brain-neurons-synapses

Humphries, C. (2015, July 7). Hugh Herr. MIT Technology Review. Retrieved from http://meche.mit.edu/people/hugh-herr

Hunt, G. L., & Hunt, M. W. (1977). Female-female pairing in western gulls *(Larus occidentalis)* in southern California. Science, 196, 1466–1467.

Hunt, G. L., Jr., Newman, A. L., Warner, M. H., Wingfield, J. C., & Kaiwi, J. (1984). Comparative behavior of male-female and female-female pairs among western gulls prior to egg laying. The Condor, 86, 157–162.

Huntington's Disease Collaborative Research Group. (1993). A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell, 72, 971–983.

Hurvich, L. M., & Jameson, D. (1957). An opponent-process theory of color vision. Psychological Review, 64, 384–404.

Husain, M., & Mehta, M. A. (2011). Cognitive enhancement by drugs in health and disease. Trends in Cognitive Sciences, 15, 28–36.

Hutchison, W. D., Davis, K. D., Lozano, A. M., Tasker, R. R., & Dostrovsky, J. O. (1999). Pain-related neurons in the human cingulate cortex. Nature Neuroscience, 2, 403–405.

Huttunen, M. (1989). Maternal stress during pregnancy and the behavior of the offspring. In S. Doxiadis (Ed.), Early influences shaping the individual (pp. 175–182). New York, NY: Plenum Press.

Hwang, B. J., Mohamed, M. A., & Brašić, J. R. (2017). Molecular imaging of autism spectrum disorder. International Review of Psychiatry, 29, 530–554.

Hyde, J. S. (2014). Gender similarities and differences. Annual Review of Psychology, 65, 373–398.

Hyman, B. T., Van Horsen, G. W., Damasio, A. R., & Barnes, C. L. (1984). Alzheimer's disease: Cell-specific pathology isolates the hippocampal formation. Science, 225, 1168–1170.

Hyman, S. E., & Malenka, R. C. (2001). Addiction and the brain: The neurobiology of compulsion and its persistence. Nature Reviews: Neuroscience, 2, 695–703.

Hyman, S. E., Malenka, R. C., & Nestler, E. J. (2006). Neural mechanisms of addiction: The role of reward-related learning and memory. Annual Review of Neuroscience, 29, 565–598.

Hyvärinen, J., & Poranen, A. (1978). Movement-sensitive cutaneous receptive fields in the hand area of the post-central gyrus in monkeys. Journal of Physiology, 283, 523–537.

IAAF Athletics. (2018, April 26). IAAF introduces new eligibility regulations for female classification. World Athletics. Retrieved from https://www.worldathletics.org/news/press-release/eligibility-regulations-for-female-classification

Iacoboni, M., Molnar-Szakacs, I., Gallese, V., Buccino, G., Mazziotta, J. C., & Giacomo, R. (2005). Grasping the intentions of others with

one's own mirror neuron system. Public Library of Science Biology, 3, 529–535.

Iacoboni, M., Woods, R. P., Brass, M., Bekkering, H., Mazziotta, J. C., & Rizzolatti, G. (1999). Cortical mechanisms of human imitation. Science, 286, 2526–2528.

Iacono, D., Markesbery, W. R., Gross, M., Pletnikova, O., Rudow, G., Zandi, P., et al. (2009). Clinically silent AD, neuronal hypertrophy, and linguistic skills in early life. Neurology, 73, 665–673.

Iacono, W. G., Carlson, S. R., Malone, S. M., & McGue, M. (2002). P3 event-related potential amplitude and the risk for disinhibitory disorders in adolescent boys. Archives of General Psychiatry, 59, 750–757.

Idänpään-Heikkilä, J., Alhava, E., Olkinuora, M., & Palva, I. P. (1977). Agranulocytosis during treatment with clozapine. European Journal of Clinical Pharmacology, 11, 193–198.

Iemmola, F., & Camperio Ciani, A. (2009). New evidence of genetic factors influencing sexual orientation in men: Female fecundity increase in the maternal line. Archives of Sexual Behavior, 38, 393–399.

Iidaka, T., Kogata, T., Mano, Y., & Komeda, H. (2019). Thalamocortical hyperconnectivity and amygdala-cortical hypoconnectivity in male patients with autism spectrum disorder. Frontiers in Psychiatry. Retrieved from https://doi.org/10.3389/fpsyt.2019.00252

Iijima, M., Arisaka, O., Minamoto, F., & Arai, Y. (2001). Sex differences in children's free drawings: A study on girls with congenital adrenal hyperplasia. Hormones and Behavior, 40, 99–104.

Immunization Safety Review Committee. (2004). Immunization safety review: Vaccines and autism. Institute of Medicine. Retrieved from https://www.nap.edu/catalog/10997.html

Imperato-McGinley, J., Peterson, R. E., Gautier, T., & Sturla, E. (1979). Androgen and the evolution of male-gender identity among male pseudohermaphrodites with 5a-reductase deficiency. New England Journal of Medicine, 300, 1233–1237.

Imperato-McGinley, J., Peterson, R. E., Stoller, R., & Goodwin, W. E. (1979). Male pseudohermaphroditism secondary to 17a-hydroxysteroid dehydrogenase deficiency: Gender role change with puberty. Journal of Clinical Endocrinology and Metabolism, 49, 391–395.

Imperato-McGinley, J., Pichardo, M., Gautier, T., Voyer, D., & Bryden, M. P. (1991). Cognitive abilities in androgen-insensitive subjects: Comparison with control males and females from the same kindred. Clinical Endocrinology, 34, 341–347.

Inda, M. C., Muravieva, E. V., & Alberini, C. M. (2011). Memory retrieval and the passage of time: From reconsolidation and strengthening to extinction. Journal of Neuroscience, 31, 1635–1643.

Inouye, S.-I. T., & Kawamura, H. (1979). Persistence of circadian rhythmicity in a mammalian hypothalamic “island” containing the suprachiasmatic nucleus. Proceedings of the National Academy of Sciences, 76, 5962–5966.

Insel, T. (2015, May 15). Post by former NIMH director Thomas Insel: Mental Health Awareness Month: By the numbers. Bethesda, MD: National Institute of Mental Health. Retrieved from https://www.nimh.nih.gov/about/directors/thomas-insel/blog/2015/mental-health-awareness-month-by-the-numbers.shtml

Insel, T. R. (1992). Toward a neuroanatomy of obsessive-compulsive disorder. Archives of General Psychiatry, 49, 739–744.

Insel, T. R., Zohar, J., Benkelfat, C., & Murphy, D. L. (1990). Serotonin in obsessions, compulsions, and the control of aggressive impulses. Annals of the New York Academy of Sciences. Special Issue: The Neuropharmacology of Serotonin, 600, 574–586.

Inta, D., Lima-Ojeda, J. M., Lau, T., Tang, W., Dormann, C., Sprengel, R., et al. (2013). Electroconvulsive therapy induces neurogenesis in frontal rat brain areas. PLoS ONE, 8, e69869. doi:10.1371/journal.pone.0069869

International Human Genome Sequencing Consortium. (2001). Initial sequencing and analysis of the human genome. Nature, 409, 860–921.

International Multiple Sclerosis Genetics Consortium. (2007). Risk alleles for multiple sclerosis identified by a genomewide study. New England Journal of Medicine, 357, 851–862.

Ishihara, K., & Sasa, M. (1999). Mechanism underlying the therapeutic effects of electroconvulsive therapy (ECT) on depression. Japanese Journal of Pharmacology, 80, 185–189.

Ising, C., Venegas, C., Zhang, S., Sheiblich, H., Schmidt, S. V., Vieira-Saecker, A., et al. (2019). NLRP3 inflammasome activation drives tau pathology. Nature, 575, 669–673.

Itani, O., Jike, M., Watanabe, N., & Kaneita, Y. (2017). Short sleep duration and health outcomes: A systematic review, meta-analysis, and meta-regression. Sleep Medicine, 32, 246–256.

Iurato, S. (1967). Submicroscopic structure of the inner ear. Oxford, UK: Pergamon Press.

Iwamura, Y., Iriki, A., & Tanaka, M. (1994). Bilateral hand representation in the postcentral somatosensory cortex. Nature, 369, 554–556.

Iwata, K. (1972). A review of the literature on drunken syndromes due to yeasts in the gastrointestinal tract (pp. 260–268). Tokyo: University of Tokyo Press.

Izawa, S., Chowdhury, S., Miyazaki, T., Mukai, Y., Ono, D., Inoue, R., et al. (2019). REM sleep-active MCH neurons are involved in forgetting hippocampus-dependent memories. Science, 365, 1308–1313.

Jackson, P. L., Meltzoff, A. N., & Decety, J. (2005). How do we perceive the pain of others? A window into the neural processes involved in empathy. NeuroImage, 24, 771–779.

Jacobs, B. L., van Praag, H., & Gage, F. H. (2000). Adult brain neurogenesis and psychiatry: A novel theory of depression. Molecular Psychiatry, 5, 262–269.

Jacobsen, J. H. W., Hutchinson, M. R., & Mustafa, S. (2016). Drug addiction: Targeting dynamic neuroimmune receptor interactions as a potential therapeutic strategy. Current Opinion in Pharmacology, 26, 131–137.

Jacquemont, S., Coe, B. P., Hersch, M., Duyzend, M. H., Krumm, N., Bergmann, S., et al. (2014). A higher mutational burden in females supports a “female protective model” in neurodevelopmental disorders. American Journal of Human Genetics, 94, 415–425.

Jaeggi, S. M., Buschkuehl, M., Jonides, J., & Shah, P. (2011). Short- and long-term benefits of cognitive training. Proceedings of the National Academy of Sciences, 108, 10081–10086.

Jain, M., Vélez, J. L., Acosta, M. T., Palacio, L. G., Balog, J., Roessler, E., et al. (2012). A cooperative interaction between *LPHN3* and 11q doubles the risk for ADHD. Molecular Psychiatry, 17, 741–747.

James, B. D., Leurgans, S. E., Hebert, L. E., Scherr, P. A., Yaffe, K., & Bennett, D. A. (2014). Contribution of Alzheimer disease to mortality in the United States. Neurology, 82, 1045–1050.

James, W. (1893). Psychology. New York, NY: Henry Holt.

Janiri, D., Moser, D. A., Doucet, G. E., Luber, M. J., Rason, A., Lee, W. H., et al. (2019). Shared neural phenotypes for mood and anxiety disorders: A meta-analysis of 226 task-related functional imaging studies. JAMA Psychiatry, 77, 172–179.

Janowsky, J. S., Oviatt, S. K., & Orwoll, E. S. (1994). Testosterone influences spatial cognition in older men. Behavioral Neuroscience, 108, 325–332.

Janszky, I., & Ljung, R. (2008). Shifts to and from daylight saving time and incidence of myocardial infarction. New England Journal of Medicine, 359, 1966–1968.

Jaretzki, A., III, Penn, A. S., Younger, D. S., Wolff, M., Olarte, M. R., Lovelace, R. E., et al. (1988). “Maximal” thymectomy for myasthenia gravis: Results. Journal of Thoracic and Cardiovascular Surgery, 95, 747–757.

Jarskog, L. F., Glantz, L. A., Gilmore, J. H., & Lieberman, J. A. (2005). Apoptotic mechanisms in the pathophysiology of

schizophrenia. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 29, 846–858.

Jeffords, J. M., & Daschle, T. (2001). Political issues in the genome era. Science, 291, 1249–1251.

Jeffrey, S. (2010, January 22). FDA approves dalfampridine to improve walking in multiple sclerosis. Medscape Medical News. Retrieved from https://www.medscape.com/viewarticle/715722

Jensen, A. R. (1969). How much can we boost IQ and scholastic achievement? Harvard Educational Review, 39, 1–123.

Jensen, A. R. (1981). Raising the IQ: The Ramey and Haskins study. Intelligence, 5, 29–40.

Jensen, A. R. (1998). The g factor. Westport, CT: Praeger.

Jike, M., Itani, O., Watanabe, N., Buysse, D. J., & Kaneita, Y. (2018). Long sleep duration and health outcomes: A systematic review, meta-analysis and meta-regression. Sleep Medicine Reviews, 39, 25–36.

Jin, K., Peel, A. L., Mao, X. O., Xie, L., Cottrell, B. A., Henshall, D. C., et al. (2004). Increased hippocampal neurogenesis in Alzheimer's disease. Proceedings of the National Academy of Sciences, 101, 343–347.

Joehanes, R., Just, A. C., Marioni, R. E., Pilling, L. C., Reynolds, L. M., Mandaviya, P. R., et al. (2016). Epigenetic signatures of cigarette smoking. Circulation: Cardiovascular Genetics. doi:10.1161//CIIRCGEENEETIICSS.116.001506

John, E. R. (2005). From synchronous neuronal discharges to subjective awareness? In S. Laureys (Ed.), The boundaries of consciousness: Neurobiology and neuropathology (pp. 143–171). New York, NY: Elsevier.

Johnson, A., & Redish, A. D. (2007). Neural ensembles in CA3 transiently encode paths forward of the animal at a decision point. Journal of Neuroscience, 27, 12176–12189.

Johnson, C., Drgon, T., McMahon, F. J., & Uhl, G. R. (2009). Convergent genome wide association results for bipolar disorder and substance dependence. American Journal of Medical Genetics, 150B, 182–190.

Johnson, J. S., & Newport, E. L. (1989). Critical period effects in second language learning: The influence of maturational state on the acquisition of English as a second language. Cognitive Psychology, 21, 60–99.

Johnson, L. A., Della Santina, C. C., & Wang, X. (2016). Selective neuronal activation by cochlear implant stimulation in auditory cortex of awake primate. Journal of Neuroscience, 36, 12468–12484.

Johnstone, T., Somerville, L. H., Alexander, A. L., Oakes, T. R., Davidson, R. J., Kalin, N. H., et al. (2005). Stability of amygdala BOLD response to fearful faces over multiple scan sessions. NeuroImage, 25, 1112–1123.

Jolles, D. D., van Buchem, M. A., Crone, E. A., & Rombouts, S. A. R. B. (2013). Functional brain connectivity at rest changes after working memory training. Human Brain Mapping, 34, 396–406.

Jonas, J. B. Schmidt, A. M., Müller-Bergh, J. A., Schlötzer-Schrehardt, U. M., & Naumann, G. O. H. (1992). Human optic

nerve fiber count and optic disc size. Investigative Ophthalmology & Visual Science, 33, 2012–2018.

Jones, B. C., Hahn, A. C., Fisher, C. I., Wang, H., Kandrik, M., & DeBruine, L. M. (2018). General sexual desire, but not desire for uncommitted sexual relationships, tracks changes in women's hormonal status. Psychoneuroendocrinology, 88, 153–157.

Jones, H. M., & Pilowsky, L. S. (2002). Dopamine and antipsychotic drug action revisited. British Journal of Psychiatry, 181, 271–275.

Jones, J. G., Tansey, E. M., & Stuart, D. G. (2011). Thomas Graham Brown (1882–1965): Behind the scenes at the Cardiff Institute of Physiology. Journal of the History of the Neurosciences, 20, 188–209.

Jones, K. L., & Smith, D. W. (1973). Recognition of the fetal alcohol syndrome in early infancy. Lancet, 2, 999–1001.

Jones, L. B., Stanwood, G. D., Reinoso, B. S., Washington, R. A., Wang, H.-Y., Friedman, E., et al. (2000). *In utero* cocaine-induced dysfunction of dopamine D1 receptor signaling and abnormal differentiation of cerebral cortical neurons. Journal of Neuroscience, 20, 4606–4614.

Jost, A. (1953). Problems of fetal endocrinology: The gonadal and hypophyseal hormones. Recent Progress in Hormone Research, 8, 379–418.

Joubert, B. R., Felix, J. F., Yousefi, P., Bakulski, K. M., Just, A. C., Breton, C., et al. (2016). DNA methylation in newborns and maternal smoking in pregnancy: Genome-wide consortium meta-analysis. American Journal of Human Genetics, 98, 680–696.

Judge, T. A., Ilies, R., & Zhang, Z. (2012). Genetic influences on core self-evaluations, job satisfaction, and work stress: A behavioral genetics mediated model. Organizational Behavior and Human Decision Processes, 117, 208–220.

Julius, D., & Basbaum, A. I. (2001). Molecular mechanisms of nociception. Nature, 413, 203–210.

Jung, R. (1974). Neuropsychologie und der Neurophysiologie des Konturund Formsehens in Zeichnung und Malerei [Neuropsychology and neurophysiology of form vision in design and painting]. In H. H. Wieck (Ed.), Psychopathologie musicher Gestaltungen (pp. 29–88). Stuttgart, Germany: Schattauer.

Jung, R. E., & Haier, R. J. (2007). The Parieto-Frontal Integration Theory (P-FIT) of intelligence: Converging neuroimaging evidence. Behavioral and Brain Sciences, 30, 135–187.

Jung, W. H., Lee, S., Lerman, C., & Kable, J. W. (2018). Amygdala functional and structural connectivity predicts individual risk tolerance. Neuron, 98, 394–404.

Kahn, M. C., Hough, G. E., Ten Eyck, G., & Bingman, V. P. (2003). Internal connectivity of the homing pigeon (*Columba livia*) hippocampal formation: An anterograde and retrograde tracer study. Journal of Comparative Neurology, 459, 1227–1241.

Kaiser, J. (2012, August 24). U.S. appeals court upholds legality of stem cell research. ScienceInsider. Retrieved from http://news.sciencemag.org/scienceinsider/2012/08/us-appeals-court-upholds-legalit.html

Kaiser, J. (2016, May 6). Gene therapy halts rare brain disease in young boys. ScienceInsider. Retrieved from http://www.sciencemag.org/news/2016/05/gene-therapy-halts-rare-brain-disease-young-boys

Kalaska J. F., & Rizzolatti, G. (2013). Voluntary movement: the primary motor cortex. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), Principles of neural science (5th ed., pp. 835–864). New York, NY: McGraw-Hill.

Kanbayashi, T., Inoue, Y., Chiba, S., Aizawa, R., Saito, Y., Tsukamoto, H., et al. (2002). CSF hypocretin-1 (orexin-A) concentrations in narcolepsy with and without cataplexy and idiopathic hypersomnia. Journal of Sleep Research, 11, 91–93.

Kandel, E. R., & O'Dell, T. J. (1992). Are adult learning mechanisms also used for development? Science, 258, 243–245.

Kandel, E. R., Schwartz, J. H., Jessell, T. M., Siegelbaum, S. A., & Hudspeth, A. J. (2013). Principles of neural science (5th ed). New York, NY: McGraw-Hill.

Kane, J. M. (1987). Treatment of schizophrenia. Schizophrenia Bulletin, 13, 133–156.

Kane, J. M., & Mertz, J. E. (2012). Debunking myths about gender and mathematics performance. Notices of the AMS, 59, 10–21.

Kanigel, R. (1988, October/November). Nicotine becomes addictive. Science Illustrated, 12–14, 19–21.

Karimi, P., Kamali, E., Mousavi, S. M., & Karahmadi, M. (2017). Environmental factors influencing the risk of autism. Journal of Research In Medical Sciences, 22, 27. Retrieved from https://www.jmsjournal.net/article.asp?issn=1735-1995;year=2017;volume=22;issue=1;spage=27;epage=27;aulast=Karimi

Karnath, H.-O., & Baier, B. (2010). Right insula for our sense of limb ownership and self-awareness of actions. Brain Structure and

Function, 214, 411–417.

Karni, A., Tanne, D., Rubenstein, B. S., Askenasy, J. J. M., & Sagi, D. (1994). Dependence on REM sleep of overnight improvement of a perceptual skill. Science, 265, 679–682.

Kashani, A. H., Lebkowski, J. S., Rahhal, F. M., Avery, R. L., Salehi-Had, H., Dang, W., et al. (2018). A bioengineered retinal pigment epithelial monolayer for advanced, dry age-related macular degeneration. Science Translational Medicine, 10(435). doi:10.1126/scitranslmed.aao4097

Kasprian, G., Langs, G., Brugger, P. C., Bittner, M., Weber, M., Arantes, M., & Prayer, D. (2010). The prenatal origin of hemispheric asymmetry: An in utero neuroimaging study. Cerebral Cortex, 21, 1076–1083.

Katan, M., Moon, Y. P., Paik, M. C., Sacco, R. L., Wright, C. B., & Elkind, M. S. V. (2013). Infectious burden and cognitive function: The Northern Manhattan Study. Neurology, 80, 1209–1215.

Kaufman, J., & Charney, D. (2000). Comorbidity of mood and anxiety disorders. Depression and Anxiety, 12(Suppl. 1), 69–76.

Kausler, D. H. (1985). Episodic memory: Memorizing performance. In N. Charness (Ed.), Aging and human performance (pp. 101–139). New York, NY: Wiley.

Kawai, N., & Matsuzawa, T. (2000). Numerical memory span in a chimpanzee. Nature, 403, 39–40.

Kaye, W., Gendall, K., & Strober, M. (1998). Serotonin neuronal function and selective serotonin reuptake inhibitor treatment in anorexia and bulimia nervosa. Biological Psychiatry, 44, 825–838.

Kaye, W. H., Frank, G. K., & McConaha, C. (1999). Altered dopamine activity after recovery from restricting-type anorexia nervosa. Neuropsychopharmacology, 21, 503–506.

Kaye, W. H., Fudge, J. L., & Paulus, M. (2009). New insights into symptoms and neurocircuit function of anorexia nervosa. Nature Reviews of Neuroscience, 10, 573–584.

Kayman, S., Bruvold, W., & Stern, J. S. (1990). Maintenance and relapse after weight loss in women: Behavioral aspects. American Journal of Clinical Nutrition, 52, 800–807.

Kazim, S. F., Blanchard, J., Bianchi, R., & Iqbal, K. (2017). Early neurotrophic pharmacotherapy rescues developmental delay and Alzheimer's-like memory deficits in the Ts65Dn mouse model of Down syndrome. Scientific Reports, 7, 45561. Retrieved from https://www.nature.com/articles/srep45561

Kearney-Ramos, T. E., Dowdle, L. T., Lench, D. H., Mithoefer, O. J., Devries, W. H., George, M. S., et al. (2018). Transdiagnostic effects of ventromedial prefrontal cortex transcranial magnetic stimulation on cue reactivity. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 3, 599–609.

Keele, S. W., & Ivry, R. (1990). Does the cerebellum provide a common computation for diverse tasks? A timing hypothesis. Annals of the New York Academy of Sciences, 608, 179–207.

Keenan, P. A., Ezzat, W. H., Ginsburg, K., & Moore, G. J. (2001). Prefrontal cortex as the site of estrogen's effect on cognition. Psychoneuroendocrinology, 26, 577–590.

Keesey, R. E., & Powley, T. L. (1986). The regulation of body weight. Annual Review of Psychology, 37, 109–133.

Kelleher, R. J., III, Govindarajan, A., & Tonegawa, S. (2004). Translational regulatory mechanisms in persistent forms of synaptic plasticity. Neuron, 44, 59–73.

Keller, K., & Menon, V. (2009). Gender differences in the functional and structural neuroanatomy of mathematical cognition. Neuroimage, 47, 342–352.

Kellner, C. H., Tobias, K. G., & Wiegand, J. (2010). Electrode placement in electroconvulsive therapy (ECT): A review of the literature. Journal of ECT, 26, 175–180.

Kellogg, W. N. (1968). Communication and language in the home-raised chimpanzee. Science, 162, 423–427.

Keltner, N. L., & Grant, J. S. (2006). Smoke, smoke, smoke that cigarette. Biological Perspectives, 42, 256–261.

Kendler, K. S., Gatz, M., Gardner, C. O., & Pedersen, N. L. (2006). A Swedish national twin study of lifetime major depression. American Journal of Psychiatry, 163, 109–114.

Kendler, K. S., MacLean, C., Neale, M., Kessler, R., Heath, A., & Eaves, L. (1991). The genetic epidemiology of bulimia nervosa. American Journal of Psychiatry, 148, 1627–1637.

Kendler, K. S., & Robinette, C. D. (1983). Schizophrenia in the National Academy of Sciences–National Research Council twin registry: A 16-year update. American Journal of Psychiatry, 140, 1551–1563.

Kennaway, D. J., & van Dorp, C. F. (1991). Free-running rhythms of melatonin, cortisol, electrolytes, and sleep in humans in Antarctica. American Journal of Physiology, 260, R1137–R1144.

Kennedy, B. K., Steffen, K. K., & Kaeberlein, M. (2007). Ruminations on dietary restriction and aging. Cellular and Molecular Life Sciences, 64, 1323–1328.

Kennerknecht, I., Grueter, T., Welling, B., Wentzek, S., Horst, J., Edwards, S., et al. (2006). First report of prevalence of non-syndromic hereditary prosopagnosia (HPA). American Journal of Medical Genetics Part A, 140A, 1617–1622.

Kern, U., Busch, V., Rockland, M., Kohl, M., & Birklein, F. (2009). Prevalence and risk factors of phantom limb pain and phantom limb sensations in Germany: A nationwide field survey. Schmerz, 23, 479–488.

Kersken, V., Gómez, J-C., Liszkowski, U., Soldati, A., & Hobaiter, C. (2019). A gestural repertoire of 1- to 2-year-old human children: In search of the ape gestures. Animal Cognition, 22, 577–595.

Kessler, R. C., Aguilar-Gaxiola, S., Alonso, J., Chatterji, S., Lee, S., Ormel, J., & Wang, P. S. (2009). The global burden of mental disorders: An update from the WHO World Mental Health (WMH) surveys. Epidemiology & Psychiatric Sciences, 18, 23–33.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distribution of DSM-IV disorders in the National Comorbidity Survey replication. Archives of General Psychiatry, 62, 593–602.

Kessler, R. C., Merikangas, K. R., & Wang, P. S. (2007). Prevalence, comorbidity, and service utilization for mood disorders in the United States at the beginning of the twenty-first century. Annual Review of Clinical Psychiatry, 3, 137–158.

Kessler, R. C., Petukhova, M., Sampson, N. A., Zaslavsky, A. M., & Wittchen, H.-U. (2012). Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United

States. International Journal of Methods in Psychiatric Research, 21, 169–184.

Kessler, R. M., Hutson, P. H., Herman, B. K., & Potenza, M. N. (2016). The neurobiological basis of binge-eating disorder. Neuroscience & Biobehavioral Reviews, 63, 223–238.

Keverne, E. B. (1999). The vomeronasal organ. Science, 286, 716–720.

Khachaturian, Z. S. (1997, July/August). Plundered memories. The Sciences, 20–25.

Khalil, A. A., Davies, B., & Castagnoli, N., Jr. (2006). Isolation and characterization of a monoamine oxidase B selective inhibitor from tobacco smoke. Bioorganic & Medicinal Chemistry, 14, 3392–3398.

Khan, T. K., & Alkon, D. L. (2010). Early diagnostic accuracy and pathophysiologic relevance of an autopsy-confirmed Alzheimer's disease peripheral biomarker. Neurobiology of Aging, 31, 889–900.

Kiang, N. Y.-S. (1965). Discharge patterns of single fibers in the cat's auditory nerve. Cambridge, MA: MIT Press.

Kidd, B. L., & Urban, L. A. (2001). Mechanisms of inflammatory pain. British Journal of Anaesthesiology, 87, 3–11.

Kieseppä, T., Partonen, T., Haukka, J., Kaprio, J., & Lönnqvist, J. (2004). High concordance of bipolar I disorder in a nationwide sample of twins. American Journal of Psychiatry, 161, 1814–1821.

Kigar, D. L., Witelson, S. F., Glezer, I. I., & Harvey, T. (1997). Estimates of cell number in temporal neocortex in the brain of Albert Einstein. Society for Neuroscience Abstracts, 23, 213.

Killin, L. O. J., Starr, J. M., Shiue, I. J., & Russ, T. C. (2016). Environmental risk factors for dementia: A systematic review. BMC Geriatrics, 16, 175. doi:10.1186/s12877-016-0342-y

Kim, J. Y., Duan, X., Liu, C. Y., Jang, M.-H., Guo, J. U., Pow-anpongkul, N., et al. (2009). DISC1 regulates new neuron development in the adult brain via modulation of AKT-mTOR signaling through KIAA1212. Neuron, 63, 761–773.

Kim, K. H. S., Relkin, N. R., Lee, K.-M., & Hirsch, J. (1997). Distinct cortical areas associated with native and second languages. Nature, 388, 171–174.

Kim, P., Evans, G. W., Angstadt, M., Ho, S. S., Sripada, C. S., Swain, E., et al. (2013). Effects of childhood poverty and chronic stress on emotion regulatory brain function in adulthood. Proceedings of the National Academy of Sciences, 110, 18442–18447.

King, B. M. (2006). The rise, fall, and resurrection of the ventromedial hypothalamus in the regulation of feeding behavior and body weight. Physiology and Behavior, 87, 221–244.

King, C., & Voruganti, L. N. P. (2002). What's in a name? The evolution of the nomenclature of antipsychotic drugs. Journal of Psychiatry and Neuroscience, 27, 168–175.

King, F. A., Yarbrough, C. J., Anderson, D. C., Gordon, T. P., & Gould, K. G. (1988). Primates. Science, 240, 1475–1482.

King, J.-R., Sitt, J. D., Faugeras, F., Rohaut, B., El Karoui, I., Cohen, L., et al. (2013). Information sharing in the brain indexes

consciousness in noncommunicative patients. Current Biology, 23, 1914–1919.

King, M.-C., & Wilson, A. C. (1975). Evolution at two levels in humans and chimpanzees. Science, 188, 107–116.

King, R. A., Leckman, J. F., Scahill, L. D., & Cohen, D. J. (1998). Obsessive-compusive disorder, anxiety, and depression. In J. F. Leckman & D. J. Cohen (Eds.), Tourette's syndrome tics, obsessions, compulsions: Developmental psychopathology and clinical care (pp. 43–62). New York, NY: Wiley.

Kinsey, A. C., Pomeroy, W. B., Martin, C. E., & Gebhard, P. H. (1953). Sexual behavior in the human female. Philadelphia, PA: Saunders.

Kipman, A., Gorwood, P., Mouren-Simeoni, M. C., & Ad'es, J. (1999). Genetic factors in anorexia nervosa. European Psychiatry, 14, 189–198.

Kirk, K. M., Bailey, J. M., Dunne, M. P., & Martin, N. G. (2000). Measurement models for sexual orientation in a community twin sample. Behavior Genetics, 30, 345–356.

Kish, D. (2013, July 12). Experience: I taught myself to see. The Guardian. Retrieved from http://www.theguardian.com/lifeandstyle/2013/jul/13/experience-blindness-echolocation-daniel-kish

Kish, S. J., Lerch, J., Furukawa, Y., Tong, J., McCluskey, T., Wilkins, D., et al. (2010). Decreased cerebral cortical serotonin transporter binding in ecstasy users: a positron emission tomography/[^{11}C]DASB and structural brain imaging study. Brain, 133, 1779–1797.

Kitamura, T., & Inokuchi, K. (2014). Role of adult neurogenesis in hippocampal-cortical memory consolidation. Molecular Brain, 7, 13. doi:10.1186/1756-6606-7-13

Kitamura, T., Ogawa, S. K., Roy, D. S., Okuyama, T., Morrissey, M. D., Smith, L. M., et al. (2017). Engrams and circuits crucial for systems consolidation of a memory. Science, 356, 73–78.

Klein, C., & Westenberger, A. (2012, January). Genetics of Parkinson's disease. Cold Spring Harbor Perspectives in Medicine, 2, a008888. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3253033

Kleinman, J. C., Pierre, M. B., Jr., Madans, J. H., Land, G. H., & Schramm, W. F. (1988). The effects of maternal smoking on fetal and infant mortality. American Journal of Epidemiology, 127, 274–282.

Klenowski, P. M., Shariff, M. R., Belmer, A., Fogarty M. J., Mu, E. W. H., Bellingham, M. C., & Bartlett, S. E. (2016). Prolonged consumption of sucrose in a binge-like manner, alters the morphology of medium spiny neurons in the nucleus accumbens shell. Frontiers in Behavioral Neuroscience, 10, Article 54. doi:10.3389/fnbeh.2016.00054

Kline, P. (1991). Intelligence: The psychometric view. New York, NY: Routledge.

Kloner, R. A., McDonald, S. A., Leeka, J., & Poole, W. K. (2011). Role of age, sex, and race on cardiac and total mortality associated with Super Bowl wins and losses. Clinical Cardiology, 34, 102–107.

Klump, K. L., Burt, A., McGue, M., & Iacono, W. G. (2007). Changes in genetic and environmental influences on disordered eating

across adolescence. Archives of General Psychiatry, 64, 1409–1415.

Knafo, A., Iervolino, A. C., & Plomin, R. (2005). Masculine girls and feminine boys: Genetic and environmental contributions to atypical gender development in early childhood. Journal of Personality and Social Psychology, 88, 400–412.

Knecht, S., Dräger, B., Deppe, M., Bobe, L., Lohmann, H., Flöel, A., et al. (2000). Handedness and hemispheric language dominance in healthy humans. Brain, 123, 2512–2518.

Knowlton, B. J., Mangels, J. A., & Squire, L. R. (1996). A neostriatal habit learning system in humans. Science, 273, 1399–1402.

Koch, K., McLean, J., Segev, R., Freed, M. A., Berry, M. J., II, Balasubramanian, V., & Sterling, P. (2006). How much the eye tells the brain. Current Biology, 16, 1428–1434.

Koch, M., Varela, L., Kim, J. G., Kim, J. D., Hernández-Nuño, F., Simonds, S. E., et al. (2015). Hypothalamic POMC neurons promote cannabinoid-induced feeding. Nature, 519, 45–50. doi:10.1038/nature14260

Koeppen, B. M., & Stanton, B. A. (2008). Berne & Levy physiology (6th ed.). Maryland Heights, MO: Mosby/Elsevier.

Koester, J., & Siegelbaum, S. A. (2013). Membrane potential and the passive electrical properties of the neuron. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), Principles of neural science (5th ed., pp. 126–147). New York, NY: McGraw-Hill.

Kogler, L., Gur, R. C., & Derntl, B. (2014). Sex differences in cognitive regulation of psychosocial achievement stress: Brain and

behavior. Human Brain Mapping, 36, 1028–1042.

Kojima, S., Nakahara, T., Nagai, N., Muranaga, T., Tanaka, M., Yasuhara, D., et al. (2005). Altered ghrelin and peptide YY responses to meals in bulimia nervosa. Clinical Endocrinology, 62, 74–78.

Komada, Y., Takaesu, Y., Matsui, K., Nakamura, M., Nishida, S., Kanno, M., et al. (2016). Comparison of clinical features between primary and drug-induced sleep-related eating disorder. Neuropsychiatric Disease and Treatment, 12, 1275–1280.

Komisaruk, B. R., Beyer, C., & Whipple, B. (2008). Orgasm. Psychologist, 21, 100–103.

Komisaruk, B. R., & Steinman, J. L. (1987). Genital stimulation as a trigger for neuroendocrine and behavioral control of reproduction. Annals of the New York Academy of Sciences, 474, 64–75.

Komisaruk, B. R., Whipple, B., Crawford, A., Grimes, S., Liu, W.-C., Kalnin, A., & Mosier, K. (2004). Brain activation during vaginocervical self-stimulation and orgasm in women with complete spinal cord injury: fMRI evidence of mediation by the vagus nerves. Brain Research, 1024, 77–88.

Kong, L.-C., Tap, J., Aron-Wisnewsky, J., Pelloux, V., Basdevant, A., Bouillot, J.-L., et al. (2013). Gut microbiota after gastric bypass in human obesity: Increased richness and associations of bacterial genera with adipose tissue genes. American Journal of Clinical Nutrition, 98, 16–24.

Koo, K. C., Ahn, J. H., Hong, S. J., Lee, J. W., & Chung, B. H. (2014). Effects of chemical castration on sexual offenders in relation to the kinetics of serum testosterone recovery: Implications for dosing schedule. Journal of Sexual Medicine, 11, 1316–1324.

Koob, G. F., & Bloom, F. E. (1988). Cellular and molecular mechanisms of drug dependence. Science, 242, 715–723.

Kopelman, M. D. (1995). The Korsakoff syndrome. British Journal of Psychiatry, 166, 154–173.

Kordasiewicz, H. B., Stanek, L. M., Wancewicz, E. V., Mazur, C., McAlonis, M. M., Pytel, K. A., et al. (2012). Sustained therapeutic reversal of Huntington's disease by transient repression of huntingtin synthesis. Neuron, 74, 1031–1044.

Kosambi, D. D. (1967, February). Living prehistory in India. Scientific American, 216, 105–114.

Koscik, T., O'Leary, D., Moser, D. J., Andreasen, N. C., & Nopoulos, P. (2009). Sex differences in parietal lobe morphology: Relationship to mental rotation performance. Brain and Cognition, 69, 451–459.

Kosslyn, S. M., Ganis, G., & Thompson, W. L. (2001). Neural foundations of imagery. Nature Reviews Neuroscience, 2, 635–642.

Koubeissi, M. Z., Bartolomei, F., Beltagy, A., & Picard, F. (2014). Electrical stimulation of a small brain area reversibly disrupts consciousness. Epilepsy & Behavior, 37, 32–35.

Koulack, D., & Goodenough, D. R. (1976). Dream recall and dream recall failure: An arousal-retrieval model. Psychological Bulletin, 83, 975–984.

Koyama, T., Tanaka, Y., & Mikami, A. (1998). Nociceptive neurons in the macaque anterior cingulate activate during anticipation of pain. NeuroReport, 9, 2663–2667.

Kraemer, H. C., Becker, H. B., Brodie, H. K. H., Doering, C. H., Moos, R. H., & Hamburg, D. A. (1976). Orgasmic frequency and plasma testosterone levels in normal human males. Archives of Sexual Behavior, 5, 125–132.

Kraepelin, E. (1921). Manic depressive insanity and paranoia (R. M. Barclay, Trans., G. M. Robertson, Ed.). Edinburgh, Scotland: E & S Livingstone.

Kramarow, E. A., & Tejada-Vera, B. (2019). Dementia mortality in the United States, 2000–2017. (2019). National Vital Statistics Reports, 68(2). Retrieved from https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_02-508.pdf

Krause, J., Lalueza-Fox, C., Orlando., L., Enard, W., Green, R. E., Burbano, H. A., et al. (2007). The derived *FOXP2* variant of modern humans was shared with Neandertals. Current Biology, 17, 1908–1912.

Krause, K.-H., Dresel, S. H., Krause, J., Kung, H. F., & Tatsch, K. (2000). Increased striatal dopamine transporter in adult patients with attention-deficit/hyperactivity disorder: Effects of methylphenidate as measured by single photon emission computed tomography. Neuroscience Letters, 285, 107–110.

Kreiman, G., Koch, C., & Fried, I. (2000). Category-specific visual responses of single neurons in the human medial temporal lobe. Nature Neuroscience, 3, 946–953.

Kriegeskorte, N., Simmons, W. K., Bellgowan, P. S. F., & Baker, C. I. (2009). Circular analysis in systems neuroscience: The dangers of double dipping. Nature Neuroscience, 12, 535–540.

Kripke, D. F., Garfinkel, L., Wingard, D. L., Klauber, M. R., & Marler, M. R. (2002). Mortality associated with sleep duration and insomnia. Archives of General Psychiatry, 59, 131–136.

Kripke, D. F., & Sonnenschein, D. (1973). A 90 minute daydream cycle [Abstract]. Sleep Research, 70, 187.

Kromer, J., Hummel, T., Pietrowski, D., Giani, A. S., Sauter, J., Ehninger, G., et al. (2016). Influence of HLA on human partnership and sexual satisfaction. Scientific Reports, 6, 32550. Retrieved from https://www.nature.com/articles/srep32550

Kruijver, F. P. M., Zhou, J.-N., Pool, C. W., Hofman, M. A., Gooren, L. J. G., & Swaab, D. F. (2000). Male-to-female transsexuals have female neuron numbers in a limbic nucleus. Journal of Clinical Endocrinology & Metabolism, 85, 2034–2041.

Kubicki, A., Leaver, A. M., Vasavada, M., Njau, S., Wade, B., Joshi, S. H. et al. (2018). Variations in hippocampal white matter diffusivity differentiate response to electroconvulsive therapy in major depression. Biological Psychiatry: Cognitive Neuroscience & Neuroimaging, 4, 300–309.

Kucher, K., Johns, D., Maier, D., Abel, R., Badke, A., Baron, H., et al. (2018). First-in-man intrathecal application of neurite growth-promoting anti-Nogo-A antibodies in acute spinal cord injury. Neurorehabilitation and Neural Repair, 32, 578–589.

Kuchinad, A., Schweinhardt, P., Seminowicz, D. A., Wood, P. B., Chizh, B. A., & Bushnell, M. C. (2007). Accelerated brain gray matter loss in fibromyalgia patients: Premature aging of the brain? Journal of Neuroscience, 27, 4004–4007.

Kudwa, A. E., Bodo, C., Gustafsson, J.-Å., & Rissman, E. F. (2005). A previously uncharacterized role for estrogen receptor: Defeminization of male brain and behavior. Proceedings of the National Academy of Sciences, 102, 4608–4612.

Kuehner, C. (2017). Why is depression more common among women than among men? Lancet Psychiatry, 4, 146–158.

Kuepper, Y., Alexander, N., Osinsky, R., Mueller, E., Schmitz, A., Netter, P., et al. (2010). Aggression—Interactions of serotonin and testosterone in healthy men and women. Behavioural Brain Research, 206, 93–100.

Kuffler, S. W. (1953). Discharge patterns and functional organization of mammalian retina. Journal of Neurophysiology, 16, 37–68.

Kuhl, P. K., & Damasio, A. (2013). Language. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), Principles of neural science (5th ed., pp. 1353–1372). New York, NY: McGraw-Hill.

Kumar, D., Kumar, V., Choi, S. H., Washicosky, K. J., Eimer, W. A., Tucker, S., et al. (2016). Amyloid-b peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. Science Translational Medicine, 8, 340ra72. doi:10.1126/scitranslmed.aaf1059

Kumari, V., & Postma, P. (2005). Nicotine use in schizophrenia: The self-medication hypotheses. Neuroscience and Biobehavioral Reviews, 29, 1021–1034.

Kupfer, D. J. (1976). REM latency: A psychobiologic marker for primary depressive disease. Biological Psychiatry, 11, 159–174.

Kurihara, K., & Kashiwayanagi, M. (1998). Introductory remarks on umami taste. Annals of the New York Academy of Sciences, 855, 393–397.

Kwak, S. S., Washicosky, K. J., Brand, E., von Maydell, D., Aronson, J., Kim, S., et al. (2020). Amyloid-β42/40 ratio drives tau pathology in 3D human neural cell culture models of Alzheimer's disease. Nature Communications, 11, 1377. Retrieved from https://www.nature.com/articles/s41467-020-15120-3

Lafee, S. (2009, November 30). H. M. recollected. San Diego Union-Tribune. Retrieved from http://www.signonsandiego.com/news/2009/nov/30/hm-recollected-famous-amnesic-launches-bold-new-br

Lai, C. S. L., Fisher, S. E., Hurst, J. A., Vargha-Khadem, F., & Monaco, A. P. (2001). A forkhead-domain gene is mutated in a severe speech and language disorder. Nature, 413, 519–523.

Lally, J., Ajnakina, O., Stubbs, B., Cullinane, M., Murphy, K. C. Gaughran, F., & Murray, R. M. (2017). Remission and recovery from first-episode psychosis in adults: Systematic review and meta-analysis of long-term outcome studies. British Journal of Psychiatry, 211, 350–358.

Lam, P., Hong, C.-J., & Tsai. S.-J. (2005). Association study of A2a adenosine receptor genetic polymorhism in panic disorder. Neuroscience Letters, 378, 98–101.

LaMantia, A. S., & Rakic, P. (1990). Axon overproduction and elimination in the corpus callosum of the developing rhesus monkey. Journal of Neuroscience, 10, 2156–2175.

Lamb, T., & Yang, J. E. (2000). Could different directions of infant stepping be controlled by the same locomotor central pattern generator? Journal of Neurophysiology, 83, 2814–2824.

Lambert, J.-C., Ibrahim-Verbaas, C. A., Harold, D., Naj, A. C., Sims, R., Bellenguez, C., et al. (2013). Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nature Genetics, 45, 1452–1458.

LaMotte, S. (2015, December 31). Woman claims her body brews alcohol, has DUI charge dismissed. CNN. Retrieved from http://www.cnn.com/2015/12/31/health/auto-brewery-syndrome-dui-womans-body-brews-own-alcohol

Lancaster, E. (1958). The final face of Eve. New York, NY: McGraw-Hill.

Landau, E. (2009, February 9). Seeing color in sounds has genetic link. CNN. Retrieved from http://www.cnn.com/2009/HEALTH/02/09/synesthesia.genes/index.html

Landry, D. W. (1997, February). Immunotherapy for cocaine addiction. Scientific American, 276, 42–45.

Landsness, E. C., Goldstein, M. R., Peterson, M. J., Tononi, G., & Benca, R. M. (2011). Antidepressant effects of selective slow wave sleep deprivation in major depression: A high-density EEG investigation. Journal of Psychiatric Research, 45, 1019–1026.

Langa, K. M. (2015). Is the risk of Alzheimer's disease and dementia declining? Alzheimer's Research and Therapy, 7, 34. doi:10.1186/s13195-015-0118-1

Langa, K. M., Larson, E. B., Crimmins, E. M., Faul, J. D., Levine, D. A., Kabeto, M. U., & Weir, D. R. (2017). A comparison of the prevalence of dementia in the United States in 2000 and 2012. JAMA Internal Medicine, 177, 51–58.

Lange, C., Deutschenbaur, L., Borgwardt, S., Lang, U. E., Walter, M., Huber, C. G., et al. (2017). Experimentally induced psychosocial stress in schizophrenia spectrum disorders: A systematic review. Schizophrenia Research, 182, 4–12.

Lange, C. G. (2010). Om Sindsbevaegelser. Whitefish, MT: Kessinger. (Original work published 1885)

Lange, N., Travers, B. G., Bigler, E. D., Prigge, M. B. D., Froehlich, A. L., Nielsen, J. A., et al. (2015). Longitudinal volumetric brain

changes in autism spectrum disorder ages 6–35 years. Autism Research, 8, 82–93.

Langer, N., Pedroni, A., Gianotti, L. R. R., Hänggi, J., Knoch, D., & Jäncke, L. (2012). Functional brain network efficiency predicts intelligence. Human Brain Mapping, 33, 1393–1406.

Langström, N., Rahman, Q., Carlström, E., & Lichtenstein, P. (2010). Genetic and environmental effects on same-sex sexual behavior: A population study of twins in Sweden. Archives of Sexual Behavior, 39, 75–80.

Lapis, T. J., Penner, M. H., & Lim, J. (2016). Humans can taste glucose oligomers independent of the hT1R2/hT1R3 sweet taste receptor. Chemical Senses. doi:10.1093/chemse/bjw088

Laplane, D., Talairach, J., Meininger, V., Bancaud, J., & Orgogozo, J. M. (1977). Clinical consequences of corticectomies involving the supplementary motor area in man. Journal of the Neurological Sciences, 34, 301–314.

Larkum, M. E. (2013). The yin and yang of cortical layer 1. Nature Neuroscience, 16, 114–115.

la Roi, C., & Mandemakers, J. J. (2018). Acceptance of homosexuality through education? Investigating the role of education, family background and individual characteristics in the United Kingdom. Social Science Research, 71, 109–128.

Larson, M. E., & Lesné, S. E. (2012). Soluble Aβ oligomer production and toxicity. Journal of Neurochemistry, 120(Suppl. 1), 125–139.

Lashley, K. (1929). Brain mechanisms and intelligence: A quantitative study of injuries to the brain. Chicago, IL: University of Chicago Press.

Laska, M. (2017). Human and animal olfactory capabilities compared. In A. Buëettner (Ed.), Springer handbook of odor (pp. 81–82). New York, NY: Springer.

Lau, B., Stanley, G. B., & Dan, Y. (2002). Computational subunits of visual cortical neurons revealed by artificial neural networks. Proceedings of the National Academy of Sciences, 99, 8974–8979.

Laureys, S. (2005). The neural correlate of (un)awareness: Lessons from the vegetative state. Trends in Cognitive Sciences, 9, 556–559.

Laureys, S., Owen, A. M., & Schiff, N. D. (2004). Brain function in coma, vegetative state, and related disorders. Lancet Neurology, 3, 537–546.

Lavie, P. (2012). Ultradian cycles in sleep propensity: Or, Kleitman's BRAC revisited. In D. Lloyd (Ed.), Ultradian rhythms in life processes (pp. 283–302). New York, NY: Springer Verlag.

Lazarini, F., & Lledo, P.-M. (2011). Is adult neurogenesis essential for olfaction? Trends in Neurosciences, 34, 20–30.

Leask, S. J. (2004). Environmental influences in schizophrenia: The known and the unknown. Advances in Psychiatric Treatment, 10, 323–330.

Lecendreux, M., Bassetti, C., Dauvilliers, Y., Mayer, G., Neidhart, E., & Tafti, M. (2003). HLA and genetic susceptibility to sleepwalking. Molecular Psychiatry, 8, 114–117.

LeDoux, J. E. (1996). The emotional brain. New York, NY: Simon & Schuster.

Lee, B. R., Ma, Y.-Y., Huang, Y. H., Wang, X., Otaka, M., Ishikawa, M., et al. (2013). Maturation of silent synapses in amygdala-accumbens projection contributes to incubation of cocaine craving. Nature Neuroscience, 16, 1644–1651.

Lee, D. S., Lee, J. S., Oh, S. H., Kim, S.-K., Kim, J.-W., Chung, J.-K., et al. (2001). Cross-modal plasticity and cochlear implants. Nature, 409, 149–150.

Lee, E.-J., Choi, S. Y., & Kim, E. (2015). NMDA receptor dysfunction in autism spectrum disorders. Current Opinion in Pharmacology, 20, 8–13.

Lee, K.-N., & Chirwa, S. (2015). Blocking dopaminergic signaling soon after learning impairs memory consolidation in guinea pigs. PLOSone. doi:10.1371/journal.pone.0135578

Lee, M., Zambreanu, L., Menon, D. K., & Tracey, I. (2008). Identifying brain activity specifically related to the maintenance and perceptual consequence of central sensitization in humans. Journal of Neuroscience, 28, 11642–11649.

Lee, M.-H., Siddoway, B., Kaeser, G. E., Segota, I., Rivera, R., Romanow, W. J., et al. (2018). Somatic APP gene recombination in Alzheimer's disease and normal neurons. Nature, 563(7733). Retrieved from https://www.nature.com/articles/s41586-018-0718-6

Lee, S., Kim, K., & Zhou, Z. J. (2010). Role of ACh-GABA cotransmission in detecting image motion and motion direction. Neuron, 68, 1159–1172.

Lee, S.-Y., Kubicki, M., Asami, T., Seidman, L. J., Goldstein, J. M., Mesholam-Gately, R. I., et al. (2013). Extensive white matter abnormalities in patients with first-episode schizophrenia: A

diffusion tensor imaging (DTI) study. Schizophrenia Research, 143, 231–238.

Lee, S. Y., Lee, A. R., Hwangbo, R., Han, J., Hong, M., & Bahn, G. H. (2015). Is oxytocin application for autism spectrum disorder evidence-based? Experimental Neurobiology, 24, 312–324.

Lefaucheur, J.-P., André-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., & Benninger, D. H. (2014). Evidence-based guidelines on the therapeutic use of repetititve transcranial magnetic stimulation (rTMS). Clinical Neurophysiology, 125, 2150–2206.

LeFoll, C., Irani, B. G., Magnan, C., Dunn-Meynell, A. A., & Levin, B. E. (2009). Characteristics and mechanisms of hypothalamic neuronal fatty acid sensing. American Journal of Physiology—Regulatory, Integrative and Comparative Physiology, 297, R655–R664.

Lehky, S. R., & Sejnowski, T. J. (1990). Neural network model of visual cortex for determining surface curvature from images of shaded surfaces. Proceedings of the Royal Society of London B, 240, 251–278.

Lehrman, S. (1999). Virus treatment questioned after gene therapy death. Nature, 401, 517–518.

Leib, D. E., Zimmerman, C. A., & Knight, Z. A. (2016). Thirst. Current Biology, 26. R1260–R1265.

Leibel, R. L., Rosenbaum, M., & Hirsch, J. (1995). Changes in energy expenditure resulting from altered body weight. New England Journal of Medicine, 332, 621–628.

Leibowitz, S. F., & Alexander, J. T. (1998). Hypothalamic serotonin in control of eating behavior, meal size, and body weight. Biological

Psychiatry, 44, 851–864.

Leinenga, G., & Götz, J. (2015). Scanning ultrasound removes amyloid-b and restores memory in an Alzheimer's disease mouse model. Science Translational Medicine, 7(278), 278ra33. doi:10.1126/scitranslmed.aaa2512

Leinenga, G., Langton, C., Nisbet, R., & Götz, J. (2016). Ultrasound treatment of neurological diseases: Current and emerging applications. Nature Reviews Neurology, 12, 161–174.

Leland, J., & Miller, M. (1998, August 17). Can gays convert? Newsweek, 47–53.

Lenneberg, E. H. (1969). On explaining language. Science, 164, 635–643.

Lenzenweger, M. F., & Gottesman, I. I. (1994). Schizophrenia. In V. S. Ramachandran (Ed.), Encyclopedia of human behavior. San Diego, CA: Academic Press.

Leonard, H. L., Lenane, M. C., Swedo, S. E., Rettew, D. C., Gershon, E. S., & Rapoport, J. L. (1992). Tics and Tourette's disorder: A 2- to 7-year follow-up of 54 obsessive-compulsive children. American Journal of Psychiatry, 149, 1244–1251.

Leonard, H. L., Lenane, M. C., Swedo, S. E., Rettew, D. C., & Rapoport, J. L. (1991). A double-blind comparison of clomipramine and desipramine treatment of severe onychophagia (nail-biting). Archives of General Psychiatry, 48, 821–826.

Leopold, D. A., & Logothetis, N. K. (1996). Activity changes in early visual cortex reflect monkeys' percepts during binocular rivalry. Nature, 379, 549–553.

Leor, J., Poole, W. K., & Kloner, R. A. (1996). Sudden cardiac death triggered by an earthquake. New England Journal of Medicine, 334, 413–419.

Le Page, Michael. (2017, October 9). Anti-doping agency to ban all gene editing in sport from 2018. New Scientist. Retrieved from https://www.newscientist.com/article/mg23631473-500-sports-crispr-ban

LePort, A. K. R., Mattfeld, A. T., Dickinson-Anson, H., Fallon, J. H., Stark, C. E. L., Kruggel, F., et al. (2012). Behavioral and neuroanatomical investigation of highly superior autobiographical memory (HSAM). Neurobiology of Learning and Memory, 98, 78–92.

LePort, A. K. R., Stark, S. M., McGaugh, J. L., & Stark, E. L. (2016). Highly superior autobiographical memory: quality and quantity of retention over time. Frontiers in Psychology, 6, 2017. Retrieved from https://www.frontiersin.org/articles/10.3389/fpsyg.2015.02017/full

Lerma-Cabrera, J. M., Carvajal, F., & Lopez-Legarrea, P. (2016). Food addiction as a new piece of the obesity framework. Nutrition Journal, 15, 5. doi:10.1186/s12937-016-0124-6.

Leshner, A. I. (1997). Addiction is a brain disease, and it matters. Science, 278, 45–47.

Leslie, M. (2019, June 6). Talk to the hand. Scientists try to debunk idea that finger length can reveal personality and health. Science. Retrieved from https://www.sciencemag.org/news/2019/06/talk-hand-scientists-try-debunk-idea-finger-length-can-reveal-personality-and-health

Lester, G. L., & Gorzalka, B. B. (1988). Effect of novel and familiar mating partners on the duration of sexual receptivity in the female

hamster. Behavioral and Neural Biology, 49, 398–405.

LeVay, S. (1991). A difference in hypothalamic structure between heterosexual and homosexual men. Science, 253, 1034–1037.

LeVay, S. (1996). Queer science: The use and abuse of research into homosexuality. Cambridge, MA: MIT Press.

Levenson, R. W., Ekman, P., & Friesen, W. V. (1990). Voluntary facial action generates emotion-specific autonomic nervous system activity. Psychophysiology, 27, 363–384.

Lévesque, M. F., Neuman, T., & Rezak, M. (2009). Therapeutic microinjection of autologous adult human neural stem cells and differentiated neurons for Parkinson's disease: Five year post-operative outcome. Open Stem Cell Journal, 1, 20–29.

Levin, F. R., Evans, S. M., & Kleber, H. D. (1998). Methylphenidate treatment for cocaine abusers with adult attention-deficit/hyperactivity disorder: A pilot study. Journal of Clinical Psychiatry, 59, 300–305.

Levin, H. S., Culhane, K. A., Hartmann, J., Evankovich, K., Mattson, A. J., Harward, H., et al. (1991). Developmental changes in performance on tests of purported frontal lobe functioning. Developmental Neuropsychology, 7, 377–395.

Levin, N., Nelson, C., Gurney, A., Vandlen, R., & de Sauvage, F. (1996). Decreased food intake does not completely account for adiposity reduction after ob protein infusion. Proceedings of the National Academy of Sciences, 93, 1726–1730.

Levine, J. A., Eberhardt, N. L., & Jensen, M. D. (1999). Role of nonexercise activity thermogenesis in resistance to fat gain in humans. Science, 283, 212–214.

Levine, J. A., Lannigham-Foster, L. M., McCrady, S. K., Krizan, A. C., Olson, L. R., Kane, P. H., et al. (2005). Interindividual variation in posture allocation: possible role in human obesity. Science, 307, 584–586.

Levy, B. (1996). Improving memory in old age through implicit self-stereotyping. Journal of Personality and Social Psychology, 71, 1092–1107.

Levy, M. (2019, January 13). The FDA is going after stem cell clinics that peddle unproven treatments. Vox. Retrieved from https://www.vox.com/2019/1/9/18173772/stem-cell-therapy-fda

Levy, S., Sutton, G., Ng, P. C., Feuk, L., Halpern, A. L., Walenz, B. P., et al. (2007). The diploid genome sequence of an individual human. PLoS Biology, 5, Article e254. Retrieved from https://www.plosbiology.org/article/info%3Adoi%2F10.1371%2Fjournal.pbio.0050254

Lewicki, P., Hill, T., & Czyzewska, M. (1992). Nonconscious acquisition of information. American Psychologist, 47, 796–801.

Lewin, R. (1980). Is your brain really necessary? Science, 210, 1232–1234.

Lewis, D. A., & Levitt, P. (2002). Schizophrenia as a disorder of neurodevelopment. Annual Review of Neuroscience, 25, 409–432.

Lewis, H. B., Goodenough, D. R., Shapiro, A., & Sleser, I. (1966). Individual differences in dream recall. Journal of Abnormal Psychology, 71, 52–59.

Lewis, J. W., Wightman, F. L., Brefczynski, J. A., Phinney, R. E., Binder, J. R., & DeYoc, E. A. (2004). Human brain regions involved

in recognizing environmental sounds. Cerebral Cortex, 14, 1008–1021.

Lewis, M., & Brooks-Gunn, J. (1979). Social cognition and the acquisition of self. New York, NY: Plenum Press.

Lewis, M. B., & Bowler, P. J. (2009). Botulinum toxin cosmetic therapy correlates with a more positive mood. Journal of Cosmetic Dermatology, 8, 24–26.

Lewis, P. D. (1985). Neuropathological effects of alcohol on the developing nervous system. Alcohol and Alcoholism, 20, 195–200.

Lewy, A. J., Sack, R. L., Miller, L. S., & Hoban, T. M. (1987). Antidepressant and circadian phase-shifting effects of light. Science, 235, 352–354.

Li, J. Z., Bunney, B. G., Meng, F., Hagenauer, M. H., Walsh, D. M., Vawter, M. P., et al. (2013). Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. Proceedings of the National Academy of Sciences, 110, 9950–9955.

Li, S., Tian, J., Bauer, A., Huang, R., Wen, H., Li, M., et al. (2016). Reduced integrity of right lateralized white matter in patients with primary insomnia: A diffusion-tensor imaging study. Radiology, 280(2). doi:10.1148/radiol.2016152038

Li, Z., Chang, S., Zhang, L., Gao, L., & Wang, J. (2014). Molecular genetic studies of ADHD and its candidate genes: A review. Psychiatry Research, 219, 10–24.

Liang, P., Xu, Y., Zhang, X., Ding, C., Huang, R., Zhang, Z., et al. (2015). CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. Protein Cell, 6, 363–372.

Lichtman, S. W., Pisarska, K., Berman, E. R., Pestone, M., Dowling, H., Offenbacher, E., et al. (1992). Discrepancy between self-reported and actual caloric intake and exercise in obese subjects. New England Journal of Medicine, 327, 1893–1898.

Lieberman, H. R., Wurtman, J. J., & Chew, B. (1986). Changes in mood after carbohydrate consumption among obese individuals. American Journal of Clinical Nutrition, 44, 772–778.

Liechti, M. E., & Vollenweider, F. X. (2000). Acute psychological and physiological effects of MDMA ("ecstasy") after haloperidol pretreatment in healthy humans. European Neuropsychopharmacology, 10, 289–295.

Lifeloc Technologies. (n.d.) BAC measurement. Retrieved from http://www.lifeloc.com/measurement.aspx

Lim, A. S. P., Klein, H.-U., Yu, L., Chibnik, L. B., Ali, S., Xu, S., et al. (2017). Diurnal and seasonal molecular rhythms in human neocortex and their relation to Alzheimer's disease. Nature Communications, 8(14931), 1–16.

Lim, M. M., Wang, Z., Olazábal, D. E., Ren, X., Terwilliger, E. F., & Young, L. J. (2004). Enhanced partner preference in a promiscuous species by manipulating the expression of a single gene. Nature, 429, 754–757.

Lin, E., & Tsai, S.-J. (2016). Genetics and suicide. In P. Courtet (Ed.), Understanding suicide (pp. 85–95). Cham, Switzerland: Springer.

Lin, L., Faraco, J., Li, R., Kadotani, H., Rogers, W., Lin, X., et al. (1999). The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell, 98, 365–376.

Linke, A. C., Keehn, R. J. J., Pueschel, E. B., Fishman, I., & Müller, R.-A. (2018). Children with ASD show links between aberrant sound processing, social symptoms, and atypical auditory interhemispheric and thalamocortical functional connectivity. Developmental Cognitive Neuroscience, 29, 117–126.

Lipton, M. L., Kim, N., Zimmerman, M. E., Kim, M., Stewart, W. F., Branch, C. A., & Lipton, R. B. (2013). Soccer heading is associated with white matter microstructural and cognitive abnormalities. Radiology, 268, 850–857.

Lisberger, S. G., & Thach, W. T. (2013). The cerebellum. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), Principles of neural science (5th ed., pp. 960–981). New York, NY: McGraw-Hill.

Lisman, J. E., Coyle, J. T., Green, R. W., Javitt, D. C., Benes, F. M., Heckers, S., & Grace, A. A. (2008). Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. Trends in Neurosciences, 31, 234–242.

Lisman, J., Grace, A. A., & Duzel, E. (2011). A neoHebbian framework for episodic memory: Role of dopamine-dependent late LTP. Trends in Neurosciences, 34, 536–547.

Lisman, J., & Morris, R. B. M. (2001). Why is the cortex a slow learner? Nature, 411, 248–249.

Liu, J., Lee, H. J., Weitz, A. J., Fang, Z., Lin, P., Choy, M., et al. (2015). Frequency-selective control of cortical and subcortical networks by central thalamus. eLife, 4, e09215. doi:10.7554/eLife.09215

Liu, L., Wang, J., Rosenberg, D. Zhao, H., Lengyel, G., & Nadel, D. (2018). Fermented beverage and food storage in 13,000 y-old

stone mortars at Raqefet Cave, Israel: Investigating Natufian ritual feasting. Journal of Archaeological Science: Reports, 21, 783–793.

Livingstone, D. (1971). Missionary travels. New York, NY: Harper & Brothers. (Original work published 1858)

Livingstone, M., & Hubel, D. (1988). Segregation of form, color, movement, and depth: Anatomy, physiology, and perception. Science, 240, 740–749.

Livingstone, M. S., Rosen, G. D., Drislane, F. W., & Galaburda, A. M. (1991). Physiological and anatomical evidence for a magnocellular defect in developmental dyslexia. Proceedings of the National Academy of Sciences, 88, 7943–7947.

Llievski, V., Zuchowska, P. K., Green, S. J., Toth, P. T., Ragozzino, M. E., Le, K., et al. (2018). Chronic oral application of a periodontal pathogen results in brain inflammation, neurodegeneration and amyloid beta production in wild type mice. PLoS One. Retrieved from https://doi.org/10.1371/journal.pone.0204941

Locurto, C. (1991). Sense and nonsense about IQ: The case for uniqueness. New York, NY: Praeger.

Loehlin, J. C., & Nichols, R. C. (1976). Heredity, environment and personality: A study of 850 twins. Austin: University of Texas Press.

Loewi, O. (1953). From the workshop of discoveries. Lawrence: University of Kansas Press.

Loftus, E. F. (1997, September). Creating false memories. Scientific American, 277, 70–75.

Logan, B. K., & Jones, A. W. (2000). Endogenous ethanol “auto-brewery syndrome” as a drunk-driving defence challenge. Medicine, Science and the Law, 40, 206–215.

Logothetis, N. K. (2002). The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. Philosophical Transactions of the Royal Society B, 357, 1003–1037.

Logue, M. W., van Rooij, S. J. H., Dennis, E. L., Davis, S. L., Hayes, J. P., Stevens, J. S., et al. (2018). Smaller hippocampal volume in posttraumatic stress disorder: A multisite ENIGMA-PGC study: Subcortical volumetry results from posttraumatic stress disorder consortia. Biological Psychiatry, 83, 244–253.

Lomber, S. G., Meredith, M. A., & Kral, A. (2010). Cross-modal plasticity in specific auditory cortices underlies visual compensations in the deaf. Nature Neuroscience, 13, 1421–1427.

London, E. D., Cascella, N. G., Wong, D. F., Phillips, R. L., Dannals, R. F., Links, J. M., et al. (1990). Cocaine-induced reduction of glucose utilization in human brain. Archives of General Psychiatry, 47, 567–574.

Loos, R. J. F., Lindgren, C. M., Li, S., Wheeler, E., Zhao, J. H., Prokopenko, I., et al. (2008). Common variants near *MC4R* are associated with fat mass, weight and risk of obesity. Nature Genetics, 40, 768–775.

Lopomo, A., Burgio, E., & Migliore, L. (2016). Epigenetics of obesity. In Y-X. Tao (Ed.), Genetics of monogenic and syndromic obesity (Vol. 140 of Progress in molecular biology and translational science, pp. 151–184). Philadelphia, PA: Elsevier.

Lorrain, D. S., Riolo, J. V., Matuszewich, L., & Hull, E. M. (1999). Lateral hypothalamic serotonin inhibits nucleus accumbens

dopamine: Implications for sexual satiety. Journal of Neuroscience, 19, 7648–7652.

Lott, I. T. (1982). Down's syndrome, aging, and Alzheimer's disease: A clinical review. Annals of the New York Academy of Sciences, 396, 15–27.

Lotze, M., Grodd, W., Birbaumer, N., Erb, M., Huse, E., & Flor, H. (1999). Does use of a myoelectric prosthesis prevent cortical reorganization and phantom limb pain? Nature Neuroscience, 2, 501–502.

Lou, H. C., Changeux, J. P., & Rosenstand, A. (2016). Towards a cognitive neuroscience of self-awareness. Neuroscience and Biobehavioral Reviews, 83, 765–773. doi:10.1016/j.neubiorev.2016.04.004

Lou, H. C., Luber, B., Stanford, A., & Lisanby, S. H. (2010). Self-specific processing in the default network: A single-pulse TMS study. Experimental Brain Research, 207, 27–38.

Louie, K., & Wilson, M. A. (2001). Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. Neuron, 29, 145–156.

Lowing, P. A., Mirsky, A. F., & Pereira, R. (1983). The inheritance of schizophrenia spectrum disorders: A reanalysis of the Danish adoptee study data. American Journal of Psychiatry, 140, 1167–1171.

Loy, B., Warner-Czyz, A. D., Tong, L., Tobey, E. A., & Roland, P. S. (2010). The children speak: An examination of the quality of life of pediatric cochlear implant users. Otolaryngology—Head and Neck Surgery, 142, 247–253.

Loyd, D. R., Wang, X., & Murphy, A. Z. (2008). Sex differences in μ-opioid receptor expression in the rat midbrain periaqueductal gray are essential for eliciting sex differences in morphine analgesia. Journal of Neuroscience, 28, 14007–14017.

Lu, T., Pan, Y., Kao, S.-Y., Li, C., Kohane, I., Chan, J., et al. (2004). Gene regulation and DNA damage in the ageing human brain. Nature, 429, 883–891.

Lu, W., Fox, P., Lakonishokl, M., Davidson, M. W., & Gelfand, V. I. (2013). Initial neurite outgrowth in Drosophila neurons is driven by kinesin-powered microtubule sliding. Current Biology, 23, 1018–1023.

Lu, W., & Gelfand, V. I. (2017). Moonlighting motors: kinesin, dynein, and cell polarity. Trends in Cell Biology, 27, 505–514.

Luber, B., Lou, H. C., Keenan, J. P., & Lisanby, S. H. (2012). Self-enhancement processing in the default network: A single-pulse TMS study. Experimental Brain Research, 223, 177–187.

Lucas, R. J., Freedman, M. S., Muñoz, M., Garcia-Fernández, J.-M., & Foster, R. G. (1999). Regulation of the mammalian pineal by non-rod, non-cone, ocular photoreceptors. Science, 284, 505–507.

Luciano, M., Wright, M., Smith, G. A., Geffen, G. M., Geffen, L. B., & Martin, N. G. (2001). Genetic covariance among measures of information processing speed, working memory, and IQ. Behavior Genetics, 31, 581–592.

Lupien, S. J., de Leon, M., de Santi, S., Convit, A., Tarshish, C., Thakur, M., et al. (1998). Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nature Neuroscience, 1, 69–73.

Lüscher, C. (2013). Drug-evoked synaptic plasticity causing addictive behavior. Journal of Neuroscience, 33, 17641–17646.

Lüscher, C. (2016). The emergence of a circuit model for addiction. Annual Review of Neuroscience, 39, 257–276.

Lüscher, C., & Malenka, R. C. (2012). NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). Cold Springs Harbor Perspectives in Biology, 4(6), a005710. doi:10.1101/cshperspect.a005710

Ly, D. H., Lockhart, D. J., Lerner, R. A., & Schultz, P. G. (2000). Mitotic misregulation and human aging. Science, 287, 2486–2492.

Lynall, R. C., Clark, M. D., Grand, E. E., Stucker, J. C., Littleton, A. C., Aguilar, A. J., et al. (2016). Head impact biomechanics in women's college soccer. Medicine & Science in Sports & Exercise (advanced online publication). Retrieved from http://journals.lww.com/acsm-msse/Abstract/publishahead/Head_Impact_Biomechanics_in_Women_s_College.97509.aspx

Lyon, L. (2009, May 8). 7 criminal cases that invoked the "sleepwalking defense." U.S. News. Retrieved from https://health.usnews.com/health-news/family-health/sleep/articles/2009/05/08/7-criminal-cases-that-invoked-the-sleepwalking-defense

Lyons, S. (2001, May 20). A will to eat, a fight for life. San Luis Obispo Tribune, p. A1.

Ma, H., Marti-Gutierrez, N., Park, S. W., Wu, J., Lee, Y., Suzuki, A., et al. (2017). Correction of a pathogenic gene mutation in human embryos. Nature, 548, doi:10.1038/nature23305

Ma, Y.-Y., Lee, B. R., Wang, X., Guo, C., Liu, L., Cui, R., et al. (2014). Bidirectional modulation of incubation of cocaine craving by silent synapse-based remodeling of prefrontal cortex to accumbens projections. Neuron, 83, 1453–1467.

Maccoby, E. E., & Jacklin, C. N. (1974). The psychology of sex differences. Stanford, CA: Stanford University Press.

Mackey, A. P., Singley, A. T., & Bunge, S. A. (2013). Intensive reasoning training alters patterns of brain connectivity at rest. Journal of Neuroscience, 33, 4796–4803.

MacNeilage, P. F. (1998). The frame/content theory of evolution of speech production. Behavioral and Brain Sciences, 21, 499–511.

Macrae, J. R., Scoles, M. T., & Siegel, S. (1987). The contribution of Pavlovian conditioning to drug tolerance and dependence. British Journal of Addiction, 82, 371–380.

Macur, J. (2012, June 25). Sex-verification policy is criticized as a failure. New York Times. Retrieved from http://www.nytimes.com/2012/06/26/sports/olympics/critics-say-olympic-sex-verification-policy-is-a-failure.html?ref=castersemenya

Maddison, D., & Viola, A. (1968). The health of widows in the year following bereavement. Journal of Psychosomatic Research, 12, 297–306.

Maeder, P. P., Meuli, R. A., Adriani, M., Bellmann, A., Fornari, E., Thiran, J.-P., et al. (2001). Distinct pathways involved in sound recognition and localization: A human fMRI study. NeuroImage, 14, 802–816.

Maes, H. H. M., Neale, M. C., & Eaves, L. J. (1997). Genetic and environmental factors in relative body weight and human adiposity. Behavior Genetics, 27, 325–351.

Maffei, M., Halaas, J., Ravussin, E., Pratley, R. E., Lee, G. H., Zhang, Y., et al. (1995). Leptin levels in human and rodent: Measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nature Medicine, 1, 1155–1161.

Magalhães, J. P., Wuttke, D., Wood, S. H., Plank, M., & Vora, C. (2012). Genome-environment interactions that modulate aging: Powerful targets for drug discovery. Pharmacological Reviews, 64, 88–101.

Magistretti, P. J., Pellerin, L., Rothman, D. L., & Shulman, R. G. (1999). Energy on demand. Science, 283, 496–497.

Magnusson, A. (2000). An overview of epidemiological studies on seasonal affective disorder. Acta Psychiatrica Scandinavica, 101, 176–184.

Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S. J., et al. (2000). Navigation-related structural change in the hippocampi of taxi drivers. Proceedings of the National Academy of Sciences, 97, 4398–4403.

Mah, L., Szabuniewicz, C., & Fiocco, A. J. (2016). Can anxiety damage the brain? Current Opinion in Psychiatry, 29, 56–63.

Maheshwari, P., & Eslick, G. D. (2015). Bacterial infection and Alzheimer's disease: A meta-analysis. Journal of Alzheimer's Disease, 43, 957–966.

Maheu, M. E., Devorak, J., Freibauer, A., Davoli, M. A., Turecki, G., & Mechawar, N. (2015). Increased doublecortin (DCX) expression and incidence of DCX-immunoreactive multipolar cells in the subventricular zone–olfactory bulb system of suicides. Frontiers in Neuroanatomy, 9, Article 74. Retrieved from http://journal.frontiersin.org/article/10.3389/fnana.2015.00074/full

Maiarù, M., Leese, C., Certo, M., Echeverria-Altuna, I., Mangione, A. S., Arsenault, J., et al. (2018). Selective neuronal silencing using synthetic botulinum molecules alleviates chronic pain in mice. Science Translational Medicine, 10, eaar7384 e1-e11.

Maier, M. A., Bennett, K. M., Hepp-Reymond, M. C., & Lemon, R. N. (1993). Contribution of the monkey corticomotoneuronal system to the control of force in precision grip. Journal of Neurophysiology, 69, 772–785.

Maier, S. F., Drugan, R. C., & Grau, J. W. (1982). Controllability, coping behavior, and stress-induced analgesia in the rat. Pain, 12, 47–56.

Mailman, R. B., & Murthy, V. (2010). Third generation antipsychotic drugs: Partial agonism or receptor functional selectivity? Current Pharmaceutical Design, 16, 488–501.

Mainz, V., Schulte-Rüther, M., Fink, G. R., Herpertz-Dahlmann, B., & Kornrad, K. (2012). Structural brain abnormalities in adolescent anorexia nervosa before and after weight recovery and associated hormonal changes. Psychosomatic Medicine, 74, 574–582.

Malenka, R. C., Nestler, E. J., & Hyman, S. E. (2009). Molecular neuropharmacology: A foundation for clinical neuroscience (2nd ed.). New York, NY: McGraw-Hill Medical.

Malhi, G. D., Tanious, M., Das, P., Coulston, C. M., & Berk, M. (2013). Potential mechanisms of action of lithium in bipolar

disorder. Current understanding. CNS Drugs, 27, 135–153.

Malison, R. T., McDougle, C. J., van Dyck, C. H., Scahill, L., Baldwin, R. M., Seibyl, J. P., et al. (1995). [123I] β-CIT SPECT imaging of striatal dopamine transporter binding in Tourette's disorder. American Journal of Psychiatry, 152, 1359–1361.

Mallikarjun, A., Shroads, E., & Newman, R. S. (2019). The cocktail party effect in the domestic dog (*Canis familiaris*). Animal Cognition, 22, 423–432.

Mamcarz, E., Zhou, S., Lockey, T., Abdelsammed, H., Cross, S. J., Pharm.D., et al. (2019). Lentiviral gene therapy combined with low-dose busulfan in infants with SCID-X1. New England Journal of Medicine, 380, 1525–1534.

Mancuso, J. J., Kim, J., Lee, S., Tsuda, S., Chow, N. B. H., & Augustine, G. J. (2010). Optogenetic probing of functional brain circuity. Experimental Physiology, 96, 26–33.

Mandel, H. (2010). Here's the deal: Don't touch me. New York, NY: Bantam Press.

Maneeton, N., Maneeton, B., Putthisri, S., Woottiluk, P., Narkpongphun, A., & Srisurapanont, M. (2018). Risperidone for children and adolescents with autism spectrum disorder: A systematic review. Neuropsychiatric Disease and Treatment, 14, 1811–1820.

Manfredi, M., Bini, G., Cruccu, G., Accornero, N., Berardelli, A., & Medolago, L. (1981). Congenital absence of pain. Archives of Neurology, 38, 507–511.

Mann, J. J. (2003). Neurobiology of suicidal behaviour. Nature Reviews Neuroscience, 4, 819–828.

Mann, J. J., Arango, V., & Underwood, M. D. (1990). Serotonin and suicidal behavior. Annals of the New York Academy of Sciences. Special Issue: The Neuropharmacology of Serotonin, 600, 476–485.

Mansari, M., Sakai, K., & Jouvet, M. (1989). Unitary characteristics of presumptive cholinergic tegmental neurons during the sleep-waking cycle in freely moving cats. Experimental Brain Research, 76, 519–529.

Mapes, G. (1990, April 10). Beating the clock: Was it an accident Chernobyl exploded at 1:23 in the morning? Wall Street Journal, p. A1.

Maquet, P., Laureys, S., Peigneux, P., Fuchs, S., Petiau, C., Phillips, C., et al. (2000). Experience-dependent changes in cerebral activation during human REM sleep. Nature Neuroscience, 3, 831–836.

Marchione, M. (2018, November 26). Chinese researcher clams first gene-edited babies. AP News. Retrieved from https://www.apnews.com/4997bb7aa36c45449b488e19ac83e86d

Marczynski, T. J., & Urbancic, M. (1988). Animal models of chronic anxiety and “fearlessness.” Brain Research Bulletin, 21, 483–490.

Marei, H. E., Hasan, A., Rizzi, R., Althani, A., Afifi, N., Cenciarelli, C., et al., (2018). Potential of stem cell-based therapy for ischemic stroke. Frontiers in Neurology. doi:10.3389/fneur.2018.00034

Mariani, J., Coppola, G., Zhang, P., Abyzov, A., Provini, L, Tomasini, L., et al. (2015). FOXG1-dependent dysregulation of GABA/glutamate neuron differentiation in autism spectrum disorders. Cell, 162, 375–390.

Marissal, T., Salazar, R. F., Bertollini, C., Mutel, S., De Roo, M., Rodriguez, I., et al. (2018). Restoring wild-type-like CA1 network dynamics and behavior during adulthood in a mouse model of schizophrenia. Nature Neuroscience, 21, 1412–1420.

Markowitz, M., Rankin, M., Mongy, M., Patino, B. E., Manusow, J., Devenyi, R. G. et al. (2018). Rehabilitation of lost functional vision with the Argus II retinal prosthesis. Canadian Journal of Ophthalmology, 53, 14–22.

Marks, D. M., Shah, M. J., Patkar, A. A., Masand, P. S., Park, G.-Y. & Pae, C.-U. (2009). Serotonin-norepinephrine reuptake inhibitors for pain control: Premise and promise. Current Neuropharmacology, 7, 331–336.

Marks, W. B., Dobelle, W. H., & MacNichol, E. F., Jr. (1964). Visual pigments of single primate cones. Science, 143, 1181–1183.

Marler, P. (1997). Three models of song learning: Evidence from behavior. Journal of Neurobiology, 33(5), 501–516.

Marler, P., & Tamura, M. (1964). Song “dialects” in three populations of white-crowned sparrows. Science, 146, 1483–1486.

Marotta, R., Risoleo, M. C., Messina, G., Parisi, L., Carotenuto, M., Vetri, L., & Rocella, M. (2020). The neurochemistry of autism. Brain Sciences, 10(3), 163. Retrieved from https://www.mdpi.com/2076-3425/10/3/163

Marshall, E. (2000). Gene therapy on trial. Science, 288, 951–957.

Marshall, J. (2008, February 16). Forgetfulness is key to a healthy mind. New Scientist, 29–33.

Martens, G., Lejeune, N., O'Brien, A. T., Fregni, F., Martial, C., Wannez, S., et al. (2018). Randomized controlled trial of home-based 4-week tDCS in chronic minimally conscious state. Brain Stimulation, 11, 982–990.

Martin, A., Haxby, J. V., Lalonde, F. M., Wiggs, C. L., & Ungerleider, L. G. (1995). Discrete cortical regions associated with knowledge of color and knowledge of actions. Science, 270, 102–105.

Martin, C. K., Bhapkar, M., Pittas, A. G., Pieper, C. F., Das, S. K., Williamson, D. A., et al. (2016). Effect of calorie restriction on mood, quality of life, sleep, and sexual function in healthy nonobese adults: The CALERIE 2 Randomized Clinical Trial. JAMA Internal Medicine, 176, 743–752.

Martin, D. S. (2008, May 16). Man's rare ability may unlock secret of memory. CNN Health. Retrieved from https://www.cnn.com/2008/HEALTH/conditions/05/07/miraculous.memory/index.html

Martin, J. B. (1987). Molecular genetics: Applications to the clinical neurosciences. Science, 238, 765–772.

Martin, M. J., Muotri, A., Gage, F., & Varki, A. (2005). Human embryonic stem cells express an immunogenic nonhuman sialic acid. Nature Medicine, 11, 228–232.

Martinez, D., & Trifilieff, P. (2014, October 14). Cocaine vaccine: Research review. American Society of Addiction Medicine Magazine. Retrieved from http://www.asam.org/magazine/read/article/2014/10/15/cocaine-vaccine-research-review

Martini, F. (1988). Fundamentals of anatomy and physiology (4th ed.). Upper Saddle River, NJ: Prentice Hall.

Martins, I. P., & Ferro, J. M. (1992). Recovery of acquired aphasia in children. Aphasiology, 6, 431–438.

Marucha, P. T., Kiecolt-Glaser, J. K., & Favagehi, M. (1998). Mucosal wound healing is impaired by examination stress. Psychosomatic Medicine, 60, 362–365.

Marx, J. (1998). New gene tied to common form of Alzheimer's. Science, 281, 507–509.

Marx, J. (2003). Cellular warriors at the battle of the bulge. Science, 299, 846–849.

Mascheretti, S., De Luca, A., Trezzi, V., Peruzzo, D., Nordio, A., Marino, C. & Arrigoni, F. (2017). Neurogenetics of developmental dyslexia: From genes to behavior through brain neuroimaging and cognitive and sensorial mechanisms. Translational Psychiatry, 7, e987.

Masica, D. N., Money, J., Ehrhardt, A. A., & Lewis, V. G. (1969). IQ, fetal sex hormones and cognitive patterns: Studies in the testicular feminizing syndrome of androgen insensitivity. Johns Hopkins Medical Journal, 124, 34–43.

Masland, R. H. (2017). Vision: Two speeds in the retina. Current Biology, 27, R303–R305.

Masters, W., & Johnson, V. (1966). The human sexual response. Boston, MA: Little, Brown.

Masterton, B., Jane, J. A., & Diamond, I. T. (1966). Role of brainstem auditory structures in sound localization: I. Trapezoid body, superior olive, and lateral lemniscus. Journal of Neurophysiology, 30(2), 341–359.

Matsuzaki, M., Honkura, N., Ellis-Davies, G. C. R., & Kasai, H. (2004). Structural basis of long-term potentiation in single dendritic spines. Nature, 429, 761–766.

Mattay, V. S., Berman, K. F., Ostrem, J. L., Esposito, G., Van Horn, J. D., Bigelow, L. B., et al. (1996). Dextroamphetamine enhances “neural network-specific” physiological signals: A positron-emission tomography rCBF study. Journal of Neuroscience, 16, 4816–4822.

Matud, M. P. (2004). Gender differences in stress and coping styles. Personality and Individual Differences, 37, 1401–1415.

Matuszewich, L., Lorrain, D. S., & Hull, E. M. (2000). Dopamine release in the medial preoptic area of female rats in response to hormonal manipulation and sexual activity. Behavioral Neuroscience, 114, 772–782.

Matyi, J. M., Rattinger, G. B., Schwartz, S., Buhusi, M., Tschanz, J. (2019). Lifetime estrogen exposure and cognition in later life: The Cache County study. Menopause, 26, 1366–1374.

Maulik, P. K., Mascarenhas, M. N., Mathers, C. D., Dua, T., & Saxena, S. (2011). Prevalence of intellectual disability: A meta-analysis of population-based studies. Research in Developmental Disabilities, 32, 419–436.

Mayer, E. A., Knight, R., Mazmanian, S. K., Cryan, J. F., & Tillisch, K. (2014). Gut microbes and the brain: Paradigm shift in neuroscience. Journal of Neuroscience, 34(46), 15490–15496. doi:10.1523/jneurosci.3299-14.2014

McAllister, E. J., Dhurandhar, N. V., Keith, S. W., Aronne, L. J., Barger, J., Baskin, M., et al. (2009). Ten putative contributors to the obesity epidemic. Critical Reviews in Food Science and Nutrition, 49, 868–913.

McCandliss, B. D., & Noble, K. G. (2003). The development of reading impairment: A cognitive neuroscience model. Mental Retardation and Developmental Disabilities Research Reviews, 9, 196–205.

McCann, U. D., Lowe, K. A., & Ricaurte, G. A. (1997). Long-lasting effects of recreational drugs of abuse on the central nervous system. Neuroscientist, 3, 399–411.

McCarthy, J. (2018, October 22). Two in three Americans now support legalizing marijuana. GALLUP News. Retrieved from https://news.gallup.com/poll/243908/two-three-americans-support-legalizing-marijuana.aspx

McClelland, J. L., McNaughton, B. L., & O'Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. Psychological Review, 102, 419–457.

McCormick, C. M., & Witelson, S. F. (1991). A cognitive profile of homosexual men compared to heterosexual men and women. Psychoneuroendocrinology, 16, 459–473.

McCormick, D. A., & Thompson, R. F. (1984). Cerebellum: Essential involvement in the classically conditioned eyelid response. Science, 223, 296–299.

McCoy, N. L., & Davidson, J. M. (1985). A longitudinal study of the effects of menopause on sexuality. Maturitas, 7, 203–210.

McDonald, J. W., Becker, D., Sadowsky, C. L., Jane, J. A., Conturo, T. E., & Schultz, L. M. (2002). Late recovery following spinal cord injury: Case report and review of the literature. Journal of Neurosurgery: Spine, 97, 252–265.

McDonald, R. J., & White, N. M. (1993). A triple dissociation of memory systems: Hippocampus, amygdala, and dorsal striatum. Behavioral Neuroscience, 107, 3–22.

McEvoy, S. P., Stevenson, M. R., McCartt, A. T., Woodward, M., Haworth, C., & Palamara, P. (2005). Role of mobile phones in motor vehicle crashes resulting in hospital attendance: A case-crossover study. British Medical Journal, 331, 428–432.

McGaugh, J. L. (2000). Memory: A century of consolidation. Science, 287, 248–251.

McGaugh, J. L., Cahill, L., & Roozendaal, B. (1996). Involvement of the amygdala in memory storage: Interaction with other brain systems. Proceedings of the National Academy of Sciences, 93, 13508–13514.

McGeoch, P. D., Brang, D., Song, T., Lee, R. R., Huang, M., & Ramachandran, V. S. (2009). Apotemnophilia: The neurological basis of a “psychological” disorder. Nature Precedings. Retrieved from http://precedings.nature.com/documents/2954/version/1

McGough, J. J., Sturm, A., Cowen, J., Tung, K., Salgari, G. C., Leuchter, A. F., et al. (2019). Double-blind, sham-controlled, pilot study of trigeminal nerve stimulation for attention-deficit/hyperactivity disorder. Child & Adolescent Psychiatry, 58, 403–411e3.

McGrath, C. L., Glatt, S. J., Sklar, P., Le-Niculescu, H., Kuczenski, R., Doyle, A. E., et al. (2009). Evidence for genetic association of *RORB* with bipolar disorder. BMC Psychiatry, 9, 70. Retrieved from https://www.biomedcentral.com/1471-244X/9/70

McGrath, J., & Saha, S. (2008). Schizophrenia: A concise overview of incidence, prevalence, and mortality. Epidemiologic Reviews, 30, 67–76.

McGue, M., & Bouchard, T. J. (1998). Genetic and environmental influences on human behavioral differences. Annual Review of Neuroscience, 21, 1–24.

McGuffin, P., Rijsdijk, F., Andrew, M., Sham, P., Katz, R., & Cardno, A. (2003). The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Archives of General Psychiatry, 60, 497–502.

McGuire, P. K., Shah, G. M. S., & Murray, R. M. (1993). Increased blood flow in Broca's area during auditory hallucinations in schizophrenia. Lancet, 342, 703–706.

McGuire, P. K., Silbersweig, D. A., Wright, I., Murray, R. M., David, A. S., Frackowiak, R. S. J., et al. (1995). Abnormal monitoring of inner speech: A physiological basis for auditory hallucinations. Lancet, 346, 596–600.

McIntosh, A. R., Rajah, M. N., & Lobaugh, N. J. (1999). Interactions of prefrontal cortex in relation to awareness in sensory learning. Science, 284, 1531–1533.

McIntyre, C. C., Grill, W. M., Sherman, D. L., & Thakor, N. V. (2004). Cellular effects of deep brain stimulation: Model-based analysis of activation and inhibition. Journal of Neurophysiology, 91, 1457–1469.

McKeefry, D. J., Gouws, A., Burton, M. P., & Morland, A. B. (2009). The noninvasive dissection of the human visual cortex: Using fMRI and TMS to study the organization of the visual cortex. Neuroscientist, 15, 489–506.

McKeith, I. (2015, November 6). Robin Williams had dementia with Lewy bodies—So what is it and why has it been eclipsed by Alzheimer's? The Conversation. Retrieved from https://theconversation.com/robin-williams-had-dementia-with-

lewy-bodies-so-what-is-it-and-why-has-it-been-eclipsed-by-alzheimers-50221

McKeon, J., McGuffin, P., & Robinson, P. (1984). Obsessive-compulsive neurosis following head injury: A report of 4 cases. British Journal of Psychiatry, 144, 190–192.

McKetin, R., Lubman, D. I., Baker, A. L., & Dawe, S. (2013). Dose-related psychotic symptoms in chronic methamphetamine users. JAMA, 70, 319–324.

McKinley, M. M., Yao, S. T., Uschakov, A., McAllen, R. M., Rundgren, M., & Martelli, D. (2015). The median preoptic nucleus: front and centre for the regulation of body fluid, sodium, temperature, sleep and cardiovascular homeostasis. Acta Physiologica, 214, 8–32.

McKinnon, W., Weisse, C. S., Reynolds, C. P., Bowles, C. A., & Baum, A. (1989). Chronic stress, leukocyte subpopulations, and humoral response to latent viruses. Health Psychology, 8, 389–402.

McLellan, T. A., Lewis, D. C., O'Brien, C. P., & Kleber, H. D. (2000). Drug dependence, a chronic medical illness: Implications for treatment, insurance, and outcomes evaluation. Journal of the American Medical Association, 284, 1689–1695.

McMahon B, Andersen, S. B., Madsen, M. K., Hjort, L. V., Hageman, I., Dam, H. et al. (2016). Seasonal difference in brain serotonin transporter binding predicts symptom severity in patients with seasonal affective disorder. Brain, 139, 1605–1614.

Mechoulam, R., Ben-Shabat, S., Hanus, L., Ligumsky, M., Kaminski, N. E., Schatz, A. R., et al. (1995). Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochemical Pharmacology, 83–90.

MediciNova. (2018a). Corporate presentation. Retrieved from https://medicinova.com/wp-content/uploads/2017/07/Medicinova_Corporate_2-21-2018.pdf

MediciNova. (2018b, March 29). MediciNova announces results of phase 2 clinical trial of MN-166 (ibudilast) in methamphetamine dependence. Intrado Globe Newswire. Retrieved from https://www.globenewswire.com/news-release/2018/03/29/1455342/0/en/MediciNova-Announces-Results-of-Phase-2-Clinical-Trial-of-MN-166-ibudilast-in-Methamphetamine-Dependence.html

Meguerditchian, A., & Vauclair, J. (2009). Contrast of hand preferences between communicative gestures and non-communicative actions in baboons: implications for the origin of hemispheric specialization for language. Brain & Language, 108, 167–174.

Meguerditchian, A., Vauclair, J., & Hopkins, W. D. (2010). Captive chimpanzees use their right hand to communicate with each other: Implications for the origin of the cerebral substrate for language. Cortex, 46, 40–48.

Meier, M. H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R. S. E., et al. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. Proceedings of the National Academy of Sciences, 109, E2657–E2664.

Meier, S. M., & Deckert, J. (2019). Genetics of anxiety disorders. Current Psychiatry Reports, 21, 1–8.

Meltzer, H. Y. (1990). Role of serotonin in depression. Annals of the New York Academy of Sciences. Special Issue: The Neuropharmacology of Serotonin, 600, 486–500.

Melzack, R. (1973). The puzzle of pain. New York, NY: Basic Books.

Melzack, R. (1992, April). Phantom limbs. Scientific American, 266, 120–126.

Melzack, R., & Wall, P. D. (1965). Pain mechanisms: A new theory. Science, 150, 971–979.

Mendez-David, I., Hen, R., Gardier, A. M., & David, D. J. (2013). Adult hippocampal neurogenesis: An actor in the antidepressant-like action. Annales Pharmaceutiques Françaises, 71, 143–149.

Mendonca, B. B., Domenice, S., Arnhold, I. J. P., & Costa, E. M. F. (2009). 46, XY disorders of sex development (DSD). Clinical Endocrinology, 70, 173–187.

Meng, M., Cherian, T., Singal, G., & Sinha, P. (2012). Lateralization of face processing in the human brain. Proceedings of the Royal Society B: Biological Sciences, 279, 2052–2061.

Meng, Q., Zhuang, Y., Ying, Z., Agrawal, R., Yang, X., & Gomez-Pinilla, F. (2017). Traumatic brain injury induces genome-wide transcriptomic, methylomic, and network perturbations in brain and blood predicting neurological disorders. EBioMedicine, 16, 184–194.

Menon, V., Rivera, S. M., White, C. D., Glover, G. H., & Reiss, A. L. (2000). Dissociating prefrontal and parietal cortex activation during arithmetic processing. NeuroImage, 12, 357–365.

Merlin, M. D. (2003). Archeological evidence for the tradition of psychoactive plant use in the Old World. Economic Botany, 57, 295–323.

Mervis, J. (2017). Data check: Federal share of basic research hits new low. Science, 355, 1005.

Merzenich, M. M., Knight, P. L., & Roth, G. L. (1975). Representation of cochlea within primary auditory cortex in the cat. Journal of Neurophysiology, 61, 231–249.

Meston, C. M., & Frohlich, P. F. (2000). The neurobiology of sexual function. Archives of General Psychiatry, 57, 1012–1030.

Mesulam, M.-M. (1986). Frontal cortex and behavior. Annals of Neurology, 19, 320–325.

Meyer-Bahlburg, H. F. L. (1984). Psychoendocrine research on sexual orientation: Current status and future options. Progress in Brain Research, 61, 375–398.

Meyer-Bahlburg, H. F. L. (2005). Gender identity outcome in female-raised 46,XY persons with penile agenesis, cloacal exstrophy of the bladder, or penile ablation. Archives of Sexual Behavior, 34, 423–438.

Meyer-Bahlburg, H. F. L., Ehrhardt, A. A., Rosen, L. R., Gruen, R. S., Veridiana, N. P., Vann, F. H., et al. (1995). Prenatal estrogens and the development of homosexual orientation. Developmental Psychobiology, 31, 12–21.

Meyer-Lindberg, A. S., Olsen, R. K., Kohn, P. D., Brown, T., Egan, M. F., Weinberger, D. R., et al. (2005). Regionally specific disturbance of dorsolateral prefrontal-hippocampal functional connectivity in schizophrenia. Archives of General Psychiatry, 62, 379–386.

Mignot, E. (1998). Genetic and familial aspects of narcolepsy. Neurology, 50(Suppl. 1), S16–S22.

Miklowitz, D. J., & Johnson, S. L. (2006). The psychopathology and treatment of bipolar disorder. Annual Review of Clinical Psychology, 2, 199–235.

Millar, J. K., Pickard, B. S., Mackie, S., James, R., Christie, S., Buchanan, S. R., et al. (2005). DISC1 and PDE4B are interacting genetic factors in schizophrenia that regulate cAMP signaling. Science, 310, 1187–1191.

Millar, J. K., Wilson-Annan, J. C., Anderson, S., Christie, S., Taylor, M. S., Semple, C. A., et al. (2000). Disruption of two novel genes by a translocation co-segregating with schizophrenia. Human Molecular Genetics, 9, 1415–1423.

Miller, A. (1967). The lobotomy patient—A decade later: A follow-up study of a research project started in 1948. Canadian Medical Association Journal, 96, 1095–1103.

Miller, B. L., Boone, K., Cummings, J. L., Read, S. L., & Mishkin, F. (2000). Functional correlates of musical and visual ability in frontotemporal dementia. British Journal of Psychiatry, 176, 458–463.

Miller, B. L., Cummings, J., Mishkin, F., Boone, K., Prince, F., Ponton, M., et al. (1998). Emergence of artistic talent in frontotemporal dementia. Neurology, 51, 978–982.

Miller, D. S., & Parsonage, S. (1975). Resistance to slimming: Adaptation or illusion? Lancet, 1, 773–775.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. Annual Review of Neuroscience, 24, 167–202.

Miller, E. K., Erickson, C. A., & Desimone, R. (1996). Neural mechanisms of visual working memory in prefrontal cortex of the Macaque. Journal of Neuroscience, 16, 5151–5167.

Miller, G. (2008). Scientists targeted in California firebombings. Science, 321, 755.

Miller, G. (2010). Beyond *DSM*: Seeking a brain-based classification of mental illness. Science, 327, 1437.

Miller, J. L., Tamura, R., Butler, M. G., Kimonis, V., Sulsona, C., Gold, J.-A., & Driscoll, D. J. (2017). Oxytocin treatment in children with Prader-Willi syndrome: A double-blind, placebo-controlled, crossover study. American Journal of Medical Genetics A, 173, 1243–1250.

Miller, N. F. (1985). The value of behavioral research on animals. American Psychologist, 40, 423–440.

Miller, S. M., Marcotulli, D., Shen, A., & Zweifel, L. S. (2019). Divergent medial amygdala projections regulate approach–avoidance conflict behavior. Nature Neuroscience, 22, 565–575.

Mills, R. (2018, June 14). Platypus venom inspires potential new diabetes treatment. Medical Press. Retrieved from https://medicalxpress.com/news/2018-06-platypus-venom-potential-diabetes-treatments.html

Milner, B. (1970). Memory and the temporal regions of the brain. In K. H. Pribram & D. E. Broadbent (Eds.), Biology and memory (pp. 29–50). New York, NY: Academic Press.

Milner, B. (1974). Hemispheric specialization: Scope and limits. In F. O. Schmitt & F. G. Worden (Eds.), The neurosciences: Third study program (pp. 75–89). Cambridge, MA: MIT Press.

Milner, B., Corkin, S., & Teuber, H.-L. (1968). Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of HM. Neuropsychologia, 6, 215–234.

Milner, P. (1977, June). How much distraction can you hear? Stereo Review, 64–68.

Miltner, W. H. R., Braun, C., Arnold, M., Witte, H., & Taub, E. (1999). Coherence of gamma-band EEG activity as a basis for associative learning. Nature, 397, 434–436.

Mineur, Y. S., Abizaid, A., Rao, Y., Salas, R., DiLeone, R. J., Gündisch, D., et al. (2011). Nicotine decreases food intake through activation of POMC neurons. Science, 332, 1330–1332.

Ming, G. L., & Song, H. (2011). Adult neurogenesis in the mammalian brain: Significant answers and significant questions. Neuron, 70, 687–702.

Miranda, A., & Taca, A. (2017). Neuromodulation with percutaneous electrical nerve field stimulation is associated with reduction in signs and symptoms of opioid withdrawal: A multisite, retrospective assessment. American Journal of Drug and Alcohol Abuse. doi:10.1080/00952990.2017.1295459

Mischkowski, D., Crocker, J., & Way, B. M. (2016). From painkiller to empathy killer: Acetaminophen (paracetamol) reduces empathy for pain. Social Cognitive and Affective Neuroscience, 11, 1345–1353.

Mishra, S. K., & Hoon, M. A. (2013). The cells and circuitry for itch responses in mice. Science, 340, 968–971.

Mitchell, D. C., Knight, C. A., Hockenberry, J., Teplansky, R., & Hartman, T. J. (2014). Beverage caffeine intakes in the U.S. Food and Chemical Toxicology, 63, 136–142.

Mitchell, K. S., Neale, M. C., Bulik, C. M., Aggen, S. H., Kendler, K. S., & Mazzeo, S. E. (2010). Binge eating disorder: A symptom-

level investigation of genetic and environmental influences on liability. Psychological Medicine, 40, 1899–1906.

Mitchell, S. W. (1866, July). The case of George Dedlow. Atlantic Monthly, 18, 1–11.

Mithoefer, M. C., Mithoefer, A. T., Feduccia, A. A., Jerome, L., Wagner, M., Wymer, J., et al. (2018). 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: A randomised, double-blind, dose-response, phase 2 clinical trial. Lancet Psychiatry, 5, 486–497.

Mitjans, M., Seidel, J., Begemann, M., Bockhop, F., Moya-Higueras, J., Bansal, V., et al. (2019). Violent aggression predicted by multiple pre-adult environmental hits. Molecular Psychiatry, 24, 1549–1564.

Mitka, M. (2006). Surgery useful for morbid obesity, but safety and efficacy questions linger. Journal of the American Medical Association, 296, 1575–1577.

Mitler, M. M., Carskadon, M. A., Czeisler, C. A., Dement, W. C., Dinges, D. F., & Graeber, R. C. (1988). Catastrophes, sleep, and public policy: Consensus report. Sleep, 11, 100–109.

Miyashita, Y. (1993). Inferior temporal cortex: Where visual perception meets memory. Annual Review of Neuroscience, 16, 245–263.

Miyashita, Y., & Chang, H. S. (1988). Neuronal correlate of pictorial short-term memory in the primate temporal cortex. Nature, 331, 68–70.

Mizutari, K., Fujioka, M., Hosoya, M., Bramhall, N., Okano, H. J., Okano, H., et al. (2013). Notch inhibition induces cochlear hair cell regeneration and recovery of hearing after acoustic trauma. Neuron, 77, 58–69.

Moffat, S. D., Zonderman, A. B., Metter, E. J., Blackman, M. R., Harman, S. M., & Resnick, S. M. (2002). Longitudinal assessment of serum-free testosterone concentration predicts memory performance and cognitive status in elderly men. Journal of Clinical Endocrinology and Metabolism, 87, 5001–5007.

Mogilner, A., Grossman, J. A. I., Ribary, U., Jolikot, M., Volkmann, J., Rapaport, D., et al. (1993). Somatosensory cortical plasticity in adult humans revealed by magnetoencephalography. Proceedings of the National Academy of Sciences, 90, 3593–3597.

Mogilnicka, E. (1981). REM sleep deprivation changes behavioral response to catecholaminergic and serotonergic receptor activation in rats. Pharmacology, Biochemistry & Behavior, 15, 149–151.

Moir, H. M., Jackson, J. C., & Windmill, J. F. C. (2013). Extremely high frequency sensitivity in a “simple” ear. Biology Letters, 9, e20130241.

Moldin, S. O., Reich, T., & Rice, J. P. (1991). Current perspectives on the genetics of unipolar depression. Behavior Genetics, 21, 211–242.

Monai, H., Ohkura, M., Tanaka, M., Oe, Y., Konno, A., Hirai, H., et al. (2016). Calcium imaging reveals glial involvement in transcranial direct current stimulation-induced plasticity in mouse brain. Nature Communications, 7, 11100. doi:10.1038/ncomms11100

Money, J. (1968). Sex errors of the body and related syndromes: A guide to counseling children, adolescents, and their families.

Baltimore, MD: Paul H. Brookes.

Money, J., Devore, H., & Norman, B. F. (1986). Gender identity and gender transposition: Longitudinal outcome study of 32 male hermaphrodites assigned as girls. Journal of Sex and Marital Therapy, 12, 165–181.

Money, J., & Ehrhardt, A. A. (1972). Man and woman, boy and girl. Baltimore, MD: Johns Hopkins University Press.

Money, J., Schwartz, M., & Lewis, V. G. (1984). Adult erotosexual status and fetal hormonal masculinization and demasculinization: 46,XX congenital virilizing adrenal hyperplasia and 46,XY androgen-insensitivity syndrome compared. Psychoneuroendocrinology, 9, 405–414.

Monteith, S. J., Gwinn, R., & Newell, D. W. (2015). A brain surgery revolution: Using sound instead of scalpels. Scientific American Mind. Retrieved from http://www.scientificamerican.com/article/a-brain-surgery-revolution-using-sound-instead-of-scalpels

Monti, M. M., Vanhaudenhuyse, A., Coleman, M. R., Boly, M., Pickard, J. D., Tshibanda, L., et al. (2010). Willful modulation of brain activity in disorders of consciousness. New England Journal of Medicine, 362, 579–589.

Montoya, E. R., Terburg, D., Bos, P. A., & van Honk, J. (2012). Testosterone, cortisol, and serotonin as key regulators of social aggression: A review and theoretical perspective. Motivation and Emotion, 36, 65–73.

Mora, F. (2013). Successful brain aging: Plasticity, environmental enrichment, and lifestyle. Dialogues in Clinical Neuroscience, 15(1), 45–52.

Moran, T. H., & Ladenheim, E. E. (2016). Physiological and neural controls of eating. Gastroenterology Clinics of North America, 45, 581–599.

Moreno, J. L., Kurita, M., Holloway, T., López, J., Cadagan, R., Martínez-Sobrido, L., et al. (2011). Maternal influenza viral infection causes schizophrenia-like alterations of 5-HT2A and mGlu2 receptors in the adult offspring. Journal of Neuroscience, 31, 1863–1872.

Moreno-Jimenez, E. P., Flor-Garcia, M., Terreros-Roncal, J., Rábano, A., Cafini, F., Pallas-Bazarra, N., et al. (2019). Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. Nature Medicine, 25, 554–560.

Moreno-Küstner, B., Martin, C., & Pastor, L. (2018). Prevalence of psychotic disorders and its association with methodological issues: A systematic review and meta-analyses. PLOS One, 13, e0195687.

Moretto, A., & Colosio, C. (2013). The role of pesticide exposure in the genesis of Parkinson's disease: Epidemiological studies and experimental data. Toxicology, 307, 24–34.

Morey, R. A., Gold, A. L., LaBar, K. S., Beall, S. K., Brown, V. M., Haswell, C. C., et al. (2012). Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. Archives of General Psychiatry, 69, 1169–1178.

Morizane, A., Doi, D., Kikuchi, T., Okita, K., Hotta, A., Kawasaki, T., et al. (2013). Direct comparison of iPSC-derived neural cells in the brain of a nonhuman primate. Stem Cell Reports, 1, 283–292.

Morrel-Samuels, P., & Herman, L. M. (1993). Cognitive factors affecting comprehension of gesture language signs: A brief

comparison of dolphins and humans. In H. L. Roitblat, L. M. Herman, & P. E. Nachtigall (Eds.), Language and communication: Comparative perspectives (pp. 311–327). Hillsdale, NJ: Lawrence Erlbaum.

Morris, J. M. (1953). The syndrome of testicular feminization in male pseudohermaphrodites. American Journal of Obstetrics and Gynecology, 65, 1192–1211.

Morris, N. M., Udry, J. R., Khan-Dawood, F., & Dawood, M. Y. (1987). Marital sex frequency and midcycle female testosterone. Archives of Sexual Behavior, 16, 27–37.

Morrison, S. F. (2016). Central neural control of thermoregulation and brown adipose tissue. Autonomic Neuroscience, 196, 14–24.

Moss, H. B., Chen, C. M., & Hsiao-ye, Y. (2007). Subtypes of alcohol dependence in a nationally representative sample. Drug and Alcohol Dependence, 91, 149–158.

Mountcastle, V. B., & Powell, T. P. S. (1959). Neural mechanisms subserving cutaneous sensibility, with special reference to the role of afferent inhibition in sensory perception and discrimination. Bulletin of the Johns Hopkins Hospital, 105, 201–232.

Mouri, A., Noda, Y., Enomoto, T., & Nabeshima, T. (2007). Phencyclidine animal models of schizophrenia: Approaches from abnormality of glutamatergic neurotransmission and neurodevelopment. Neurochemistry International, 51, 173–184.

Mouritsen, H., Janssen-Bienhold, U., Liedvogel, M., Feenders, G., Stalleicken, J., Dirks, P., et al. (2004). Cryptocromes and neuronal-activity markers colocalize in the retina of migratory birds during magnetic orientation. Proceedings of the National Academy of Sciences, 101, 14297.

Mpakopoulou, M., Gatos, H., Brotis, A., Paterakis, K. N., & Fountas, K. N. (2008). Stereotactic amygdalotomy in the management of severe aggressive behavioral disorders. Neurosurgery Focus, 42, E3. doi:10.3171/2016.10.FOCUS16411

Mühleisen, T. W., Leber, M., Schulze, T. G., Strohmaier, J., Degenhardt, F., Treutlein, J., et al. (2014). Genome-wide association study reveals two new risk loci for bipolar disorder. Nature Communications, 5, 3339. Retrieved from http://www.nature.com/ncomms/2014/140311/ncomms4339/full/ncomms4339.html

Mulle, J. G., Pulver, A. E., McGrath, J. A., Wolyniec, P. S., Dodd, A. F., Cutler, D. J., et al. (2014). Reciprocal duplication of the Williams-Beuren syndrome deletion on chromosome 7q11.23 is associated with schizophrenia. Biological Psychiatry, 75, 371–377.

Müller, U. (2008). Cadherins and mechanotransduction by hair cells. Current Opinion in Cell Biology, 20, 557–566.

Muraro, P. A., Pasquini, M., Atkins, H. L., Bowen, J. D., Farge, D., Fassas, A., et al. (2017). Long-term outcomes after autologous hematopoietic stem cell transplantation for multiple sclerosis. JAMA Neurology, 74(4), 459–469. doi:10.1001/jamaneurol.2016.5867

Murphy, G. (1949). Historical introduction to modern psychology. New York, NY: Harcourt, Brace & World.

Murphy, M. R., Checkley, S. A., Seckl, J. R., & Lightman, S. L. (1990). Naloxone inhibits oxytocin release at orgasm in man. Journal of Clinical Endocrinology and Metabolism, 71, 1056–1058.

Murray, R. M., & Lewis, S. W. (1987). Is schizophrenia a neurodevelopmental disorder? British Journal of Medicine, 295, 681–682.

Murrell, J., Farlow, M., Ghetti, B., & Benson, M. D. (1991). A mutation in the amyloid precusor protein associated with hereditary Alzheimer's disease. Science, 254, 97–99.

Murrough, J. W., Iosifescu, D. V., Chang, L. C., Al Jurdi, R. K., Green, C. E., Perez, A. M., et al. (2013). Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site randomized controlled trial. American Journal of Psychiatry, 170(10), 1134–1142.

Must, A., Spadano, J., Coakley, E. H., Field, A. E., Colditz, G., & Dietz, W. H. (1999). The disease burden associated with overweight and obesity. Journal of the American Medical Association, 282, 1523–1529.

Mustanski, B. S., DuPree, M. G., Nievergelt, C. M., Bocklandt, S., Schork, N. J., & Hamer, D. H. (2005). A genomewide scan of male sexual orientation. Human Genetics, 116, 272–278.

Mutz, J., Vipulananthan, V., Carter, B., Hurlemann, R., Fu, C. H. Y., Young, A. H., et al. (2019). Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: Systematic review and network meta-analysis. BMJ, 364, el1079.

Nachev, P., Lopez-Sosa, F., Gonzalez-Rosa, J. J., Galarza, A., Avecillas, J., Pineda-Pardo, J. A., et al. (2015). Dynamic risk control by human nucleus accumbens. Brain, 138, 3496–3502.

Nader, K., Schafe, G. E., & LeDoux, J. E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature, 406, 722–726.

Naglieri, J. A., & Ronning, M. E. (2000). Comparison of white, African American, Hispanic, and Asian children on the Naglieri nonverbal ability test. Psychological Assessment, 12, 328–334.

Nair, A., Carper, R. A., Abbott, A. E., Chen, C. P., Solders, S., Nakutin, S., et al. (2015). Regional specificity of aberrant thalamocortical connectivity in autism. Human Brain Mapping, 36, 4497–4511.

Nairne, J. S. (2000). Psychology: The adaptive mind (2nd ed.). Belmont, CA: Wadsworth/Thomson Learning.

Nakashima, T., Pierau, F. K., Simon, E., & Hori, T. (1987). Comparison between hypothalamic thermoresponsive neurons from duck and rat slices. Pflugers Archive: European Journal of Physiology, 409, 236–243.

Naliboff, B., Berman, S., Chang, L., Derbyshire, S., Suyenobu, B., Vogt, B., et al. (2003). Sex-related differences in IBS patients: Central processing of visceral stimuli. Gastroenterology, 124, 1738–1747.

Nanda, P., Tandon, N., Mathew, I. T., Giakoumatos, C. I., Abhishekh, H. A., Clementz, B. A., et al. (2014). Local gyrification index in probands with psychotic disorders and their first-degree relatives. Biological Psychiatry, 76, 447–455.

Narr, K. L., Woods, R. P., Thompson, P. M., Szeszko, P., Robinson, D., Dimtcheva, T., et al. (2007). Relationships between IQ and regional cortical gray matter thickness in healthy adults. Cerebral Cortex, 17, 2163–2171.

Narvaes, R., & de Almeida, R. M. M. (2014). Aggressive behavior and three neurotransmitters: Dopamine, GABA, and serotonin—A review of the last 10 years. Psychology & Neuroscience, 7, 601–607.

Nash, J. M., Park, A., & Willwerth, J. (1995, July 17). “Consciousness” may be an evanescent illusion. Time, p. 52.

National Academy of Sciences and National Academy of Medicine. (2017, February 14). With stringent oversight, heritable human genome editing could be allowed for serious conditions. Retrieved from http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=24623

National Highway Traffic Safety Administration. (2015). Traffic safety facts 2014 data: Alcohol-impaired driving. Retrieved from https://crashstats.nhtsa.dot.gov/Api/Public/ViewPublication/812231

National Human Genome Research Institute. (2016, January 7). The genotype-tissue expression project (GTEx). Retrieved from https://www.genome.gov/gtex/

National Institute of Mental Health. (1986). Schizophrenia: Questions and answers (DHHS Publication No. ADM 86-1457). Washington, DC: U.S. Government Printing Office.

National Institute of Mental Health. (2019a). Mental illness. Retrieved from https://www.nimh.nih.gov/health/statistics/mental-illness.shtml

National Institute of Mental Health. (2019b). Suicide. Retrieved from https://www.nimh.nih.gov/health/statistics/suicide.shtml

National Institute on Alcohol Abuse and Alcoholism. (2016, January). Alcohol facts and statistics. Retrieved from https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-facts-and-statistics

National Institute on Drug Abuse. (2012, October). Drug facts: Understanding drug abuse and addiction. Retrieved from http://www.drugabuse.gov/publications/drugfacts/understanding-drug-abuse-addiction

National Institute on Drug Abuse. (2014). Principles of adolescent substance use disorder treatment: A research guide. Retrieved from https://www.drugabuse.gov/publications/principles-adolescent-substance-use-disorder-treatment-research-based-guide/evidence-based-approaches-to-treating-adolescent-substance-use-disorders/addiction-medications

National Institute on Drug Abuse. (2018). Is drug addiction treatment worth its cost? Retrieved from https://www.drugabuse.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition/frequently-asked-questions/drug-addiction-treatment-worth-its-cost

National Institute on Drug Abuse. (n.d.). Trends and statistics. Retrieved from https://www.drugabuse.gov/related-topics/trends-statistics#supplemental-references-for-economic-costs

National Institutes of Health. (2015). Public Health Service policy on humane care and use of laboratory animals (NIH Publication No. 15-8013). Retrieved from https://olaw.nih.gov/sites/default/files/PHSPolicyLabAnimals.pdf

National Sleep Foundation. (2002). 2002 “Sleep in America” poll. Retrieved from https://www.sleepfoundation.org/sites/default/files/inline-files/2002SleepInAmericaPoll.pdf

NCD Risk Factor Collaboration. (2016). Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet, 387, 1377–1396.

NCD Risk Factor Collaboration. (2017). Trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: A pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet, 390, 2627–2642.

Nebes, R. D. (1974). Hemispheric specialization in commissurotomized man. Psychological Bulletin, 81, 1–14.

Neisser, U., Boodoo, G., Bouchard, T. J., Jr., Boykin, A. W., Brody, N., Ceci, S. J., et al. (1996). Intelligence: Knowns and unknowns. American Psychologist, 51, 77–101.

Nelson, D. A. (2000). Song overproduction, selective attrition and song dialects in the white-crowned sparrow. Animal Behaviour, 60, 887–898.

Nelson, L. (2004). Venomous snails: One slip, and you're dead … Nature, 429, 798–799.

Nelson, R. J., & Trainor, B. C. (2007). Neural mechanisms of aggression. Nature Reviews Neuroscience, 8, 536–546.

Netter, F. H. (1983). CIBA collection of medical illustrations: Vol. 1. Nervous system. New York, NY: CIBA.

Neville, H. J., Bavelier, D., Corina, D., Rauschecker, J., Karni, A., Lalwani, A., et al. (1998). Cerebral organization for language in deaf and hearing subjects: Biological constraints and effects of experience. Proceedings of the National Academy of Sciences, 95, 922–929.

Newbury, D. F., Fisher, S. E., & Monaco, A. P. (2010). Recent advances in the genetics of language impairment. Genome Medicine, 2(6). Retrieved from http://genomemedicine.com/content/2/1/6

Newman, E. A. (2003). New roles for astrocytes: Regulation of synaptic transmission. Trends in Neurosciences, 26, 536–542.

Newport, F. (2015, May 21). Americans greatly overestimate percent gay, lesbian in U.S. Gallup. Retrieved from http://www.gallup.com/poll/183383/americans-greatly-overestimate-percent-gay-lesbian.aspx

Ng, S. W., & Popkin, B. M. (2012). Time use and physical activity: A shift away from movement across the globe. Obesity Reviews, 13, 659–680.

Ngun, T. C., & Vilain, E. (2014). The biological basis of human sexual orientation: Is there a role for epigenetics? Advances in Genetics, 86, 167–184.

Nguyen, H. B., Loughead, J., Lipner, E., Hantsoo, L., Kornfield, S. L., & Epperson, C. N. (2019). What has sex got to do with it? The role of hormones in the transgender brain. Neuropsychopharmacology, 44, 22–37.

Nichelli, P., Grafman, J., Pietrini, P., Clark, K., Lee, K. Y., & Miletich, R. (1995). Where the brain appreciates the moral of a story. Neuroreport, 6, 2309–2313.

Nicoll, R. A., & Madison, D. V. (1982). General anesthetics hyperpolarize neurons in the vertebrate central nervous system. Science, 217, 1055–1057.

Nield, D. (2016, June 3). The first gene therapy for children has just been approved in Europe. ScienceAlert. Retrieved from http://www.sciencealert.com/first-gene-therapy-for-children-is-approved-in-europe

Nielsen, A. S., Mortensen, P. B., O'Callaghan, E., Mors, O., & Ewald, H. (2002). Is head injury a risk factor for schizophrenia? Schizophrenia Research, 55, 93–98.

Nieto, F. R., Cobos, E. J., Tejada, M. A., Sanchez-Fernando, C., Gonzalez-Cano, R., & Cendan, C. M. (2012). Tetrodotoxin (TTX) as a therapeutic agent for pain. Marine Drugs, 10, 281–305.

Nigg, J. T., Elmore, A. L., Natarajan, N., Friderici, K. H., & Nikolas, M. A. (2016). Variation in an iron metabolism gene moderates the association between blood lead levels and attention-deficit/hyperactivity disorder in children. Psychological Science, 27, 257–269.

Nigg, J. T., Nikolas, M., Knottnerus, G. M., Cavanagh, K., & Friderici, K. (2010). Confirmation and extension of association of blood lead with attention-deficit/hyperactivity disorder (ADHD) and ADHD symptom domains at population-typical exposure levels. Journal of Child Psychology and Psychiatry, 51, 58–65.

Niimura, Y., Matsui, A., & Touhara, K. (2016). Extreme expansion of the olfactory receptor gene repertoire in African elephants and evolutionary dynamics of orthologous gene groups in 13 placental mammals. Genome Research, 24, 1485–1496. doi:10.1101/gr.169532.113

Nimkarn, S., & New, M. I. (2010). Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: A paradigm for prenatal diagnosis and treatment. Annals of the New York Academy of Sciences, 1192, 5–11.

Nisbett, R. E. (2005). Heredity, environment, and race differences in IQ: A commentary on Rushton and Jensen. Psychology, Public Policy, and Law, 11, 302–310.

Nishitani, N., Avikainen, S., & Hari, R. (2004). Abnormal imitation-related cortical activation sequences in Asperger's syndrome. Annals of Neurology, 55, 558–562.

Nobili, L., Ferrillo, F., Besset, A., Rosadini, G., Schiavi, G., & Billiard, M. (1996). Ultradian aspects of sleep in narcolepsy. Neurophysiologie Clinique, 26, 51–59.

Nori, S., Ahuja, C. S., & Fehlings, M. G. (2017). Translational advances in the management of acute spinal cord injury: What is new? What is hot? Neurosurgery, 64, 119–128.

Normile, D. (2019, December 30). Chinese scientist who produced genetically altered babies sentenced to 3 years in jail. Science. Retrieved from https://www.sciencemag.org/news/2019/12/chinese-scientist-who-produced-genetically-altered-babies-sentenced-3-years-jail

Nottebohm, F. (1977). Asymmetries in neural control of vocalization in the canary. In S. Harnad, R. W. Doty, L. Goldstein, J. Jaynes, & G. Krauthamer (Eds.), Lateralization in the nervous system (pp. 23–44). New York, NY: Academic Press.

Novati, A., Hulshof, H. J., Granic, I., & Meerlo, P. (2012). Chronic partial sleep deprivation reduces brain sensitivity to glutamate N-methyl-D-aspartate receptor-mediated neurotoxicity. Journal of Sleep Research, 21, 3–9.

Nulman, I., Rovet, J., Greenbaum, R., Loebstein, M., Wolpin, J., Pace-Asciak, P., et al. (2001). Neurodevelopment of adopted children exposed in utero to cocaine: The Toronto adoption study. Clinical and Investigative Medicine, 24, 129–137.

Nunn, J. A., Gregory, L. J., Brammer, M., Williams, S. C. R., Parslow, D. M., Morgan, M. J., et al. (2002). Functional magnetic resonance imaging of synesthesia: Activation of V4/V8 by spoken words. Nature Neuroscience, 5, 371–375.

Nussbaum, R. L., & Ellis, C. E. (2003). Alzheimer's disease and Parkinson's disease. New England Journal of Medicine, 348,

1356–1364.

Oberman, L. M., Winkielman, P., & Ramachandran, V. S. (2007). Face to face: Blocking facial mimicry can selectively impair recognition of emotional expressions. Social Neuroscience, 2, 167–178.

Oberman, L. M., Winkielman, P., & Ramachandran, V. S. (2009). Slow echo: Facial EMG evidence for the delay of spontaneous, but not voluntary, emotional mimicry in children with autism spectrum disorders. Developmental Science, 12, 510–520.

O'Brien, C. P. (1997). A range of research-based pharmacotherapies for addiction. Science, 278, 66–70.

O'Brien, N. L., Way, M. L., Kandaswamy, R., Fiorentino, A., Sharp, S. I., Wuadri, G., et al. (2014). The functional GRM3 Kozak sequence variant rs148754219 affects the risk of schizophrenia and alcohol dependence as well as bipolar disorder. Psychiatric Genetics, 24, 277–278.

Ocklenburg, S., Friedrich, P., Fraenz, C., Sclüter, C., Beste, C., Güntürk, O., et al. (2018). Neurite architecture of the planum temporale predicts neurophysiological processing of auditory speech. Science Advances, 4(7), eaar6830. doi:0.1126/sciadv.aar6830

O'Connor, D. H., Fukui, M. M., Pinsk, M. A., & Kastner, S. (2002). Attention modulates responses in the human lateral geniculate nucleus. Nature Neuroscience, 5, 1203–1209.

O'Connor, J. (2019, June 25). Illinois becomes 11th state to allow recreational marijuana. AP News. Retrieved from https://www.apnews.com/7b793d88f3c84417b83db0f770854960

Ogden, J. (1989). Visuospatial and other “right-hemispheric” functions after long recovery periods in left-hemispherectomized subjects. Neuropsychologia, 27, 765–776.

O’Keane, V., & Dinan, T. G. (1992). Sex steroid priming effects on growth hormone response to pyridostigmine throughout the menstrual cycle. Journal of Clinical Endocrinology and Metabolism, 75, 11–14.

Okubo, Y., Suhara, T., Suzuki, K., Kobayashi, K., Inoue, O., Terasaki, O., et al. (1997). Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. Nature, 385, 634–636.

Okun, M. S., Foote, K. D., Wu, S. S., Ward, H. E., Bowers, D., Rodriguez, R. L., et al. (2013). A trial of scheduled deep brain stimulation for Tourette syndrome. JAMA Neurology, 70, 85–94.

Olanow, C. W., & Tatton, W. G. (1999). Etiology and pathogenesis of Parkinson’s disease. Annual Review of Neuroscience, 22, 123–144.

Olds, J., & Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. Journal of Comparative and Physiological Psycholology, 47, 419–427.

Olender, T., Waszak, S. M., Viavant, M., Khen, M., Ben-Asher, E., Reyes, A., et al. (2012). Personal receptor repertoires: Olfaction as a model. BMC Genomics, 13(414). Retrieved from http://www.biomedcentral.com/1471-2164/13/414

Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H.-U., & Jönsson, B. (2011). The economic cost of brain disorders in Europe. European Journal of Neurology, 19, 155–162.

Oliet, S. H. R., Piet, R., & Poulain, D. A. (2001). Control of glutamate clearance and synaptic efficacy by glial coverage of neurons. Science, 292, 923–925.

Oliviera, B. M., & Teichert, R. W. (2007). Diversity of the neurotoxic conus peptides: A model for concerted pharmacological discovery. Molecular Interventions, 7, 251–260.

Olsen, C. M. (2011). Natural rewards, neuroplasticity, and non-drug addictions. Neuropharmacology, 61, 1109–1122.

Olshansky, S. J., Antonucci, T., Berkman, L., Binstock, R. H., Boersch-Supan, A., Cacioppo, J. T., et al. (2012). Differences in life expectancy due to race and educational differences are widening, and many may not catch up. Health Affairs, 31, 1803–1813.

Olson, E. J., Boeve, B. F., & Silber, M. H. (2000). Rapid eye movement sleep behaviour disorder: Demographic, clinical and laboratory findings in 93 cases. Brain, 123, 331–339.

Olulade, O. A., Napoliello, E. M., & Eden, G. F. (2013). Abnormal visual motion processing is not a cause of dyslexia. Neuron, 79, 180–190.

Onstad, S., Skre, I., Torgersen, S., & Kringlen, E. (1991). Twin concordance for DSM-III-R schizophrenia. Acta Psychiatria Scandinavica, 83, 395–401.

Oo, K. Z., Aung, Y. K., Jenkins, M. A., & Win, A. K. (2016). Associations of 5HTTLPR polymorphism with major depressive disorder and alcohol dependence: A systematic review and meta-analysis. Australia and New Zealand Journal of Psychiatry, 50, 842–857.

O'Reilly, K. B. (2018, October 24). 10 ways the new opioids law could help address the epidemic. American Medical Association. Retrieved from https://www.ama-assn.org/delivering-care/opioids/10-ways-new-opioids-law-could-help-address-epidemic

Orlans, F. B. (1993). In the name of science. New York, NY: Oxford University Press.

Orlovska, S., Pedersen, M. S., Benros, M. R., Mortensen, P. B., Agerbo, E., & Nordentoft, M. (2014). Head injury as risk factor for psychiatric disorders: A nationwide register-based follow-up study of 113,906 persons with head injury. American Journal of Psychiatry, 171(4), 463–469.

O'Rourke, D., Wurtman, J. J., Wurtman, R. J., Chebli, R., & Gleason, R. (1989). Treatment of seasonal depression with *d*-fenfluramine. Journal of Clinical Psychiatry, 50, 343–347.

Ortiz-Catalan, M. (2018). The stochastic entanglement and phantom motor execution hypotheses: A theoretical framework for the origin and treatment of phantom limb pain. Frontiers in Neurology, 9, Article 748. doi:10.3389/fneur.2018.00748

Ortiz-Catalan, M., Guðmundsdóttir, R. A., Kristoffersen, M. B., Zepeda-Echavarria, A., Caine-Winterberger, K., Kulbacka-Ortiz, K., et al. (2016). Phantom motor execution facilitated by machine learning and augmented reality as treatment for phantom limb pain: A single group, clinical trial in patients with chronic intractable phantom limb pain. Lancet, 388, 2885–2894.

Osvath, M. (2009). Spontaneous planning for future stone throwing by a male chimpanzee. Current Biology, 19, R190–R191.

Oviedo-Joekes, E., Guh, D., Brissette, S., Marchand, K., MacDonald, S., Lock, K., et al. (2016). Hydromorphone compared with

diacetylmorphine for long-term opioid dependence: A randomized trial. JAMA Psychiatry, 73, 447–455.

Owens, N., & McGorry, P. D. (2003). Seasonality of symptom onset in first-episode schizophrenia. Psychological Medicine, 33, 163–167.

Ozbay, F., Johnson, D. C., Dimoulas, E., Morgan, C. A. III, Charney, D., & Southwick, S. (2007). Social support and resilience to stress. Psychiatry, 4, 35–40.

Paean to Nepenthe. (1961, November 24). Time, p. 68.

Palfi, S., Gurruchaga, J. M., Lepetit, H., Howard, K., Ralph, G. S., Mason, S., et al. (2018). Long-term follow-up of a phase I/II study of ProSavin, a lentiviral vector gene therapy for Parkinson's Disease. Human Gene Therapy Clinical Development, 29, 148–155.

Palmer, A. R. (1987). Physiology of the cochlear nerve and cochlear nucleus. In M. P. Haggard & E. F. Evans (Eds.), Hearing (pp. 838–855). Edinburgh, UK: Churchill Livingstone.

Panda, S., Nayak, S. K., Campo, B., Walker, J. R., Hogenesch, J. B., & Jegla, T. (2005). Illumination of the melanopsin signaling pathway. Science, 307, 600–604.

Pandarinath, C., Nuyujukian, P., Blabe, C. H., Sorice, B. L., Saab, J., Willett, F. R., et al. (2017). High performance communication with paralysis using an intracortical brain-computer interface. eLIFE, 6, e18554. doi:10.7554/eLife.18554

Pandey, M., Zhang, J.-H., Mishra, S. K., Adikaram, P. R., Harris, B., Kahler, J. F., et al. (2017). A central role for R7bp in the regulation of itch. Pain, 158(5), 931–944.

Papalambros, N. A., Santostasi, G., Malkani, R. G., Braun, R., Weintraub, S., Paller, K. A., & Zee, P. C. (2017). Acoustic enhancement of sleep slow oscillations and concomitant memory improvement in older adults. Frontiers in Human Neuroscience, 11, 109. doi:10.3389/fnhum.2017.00109

Pappone, P. A., & Cahalan, M. D. (1987). *Pandinus imperator* scorpion venom blocks voltage-gated potassium channels in nerve fibers. Journal of Neuroscience, 7, 3300–3305.

Paquin, S., Lacourse, E., Brendgen, M., Vitaro, F., Dione, G., Tremblay, R. E., & Boivin, M. (2017). Heterogeneity in the development of proactive and reactive aggression in childhood: Common and specific genetic-environmental factors. PLoS One, 12(12), e0188730. Retrieved from https://doi.org/10.1371/journal.pone.0188730

Parent, J. M. (2003). Injury-induced neurogenesis in the adult mammalian brain. Neuroscientist, 9, 261–272.

Park, B. (2020, March). Treatment of moderate to severe osteoarthritis pain. Rheumatology Advisor. Retrieved from https://www.rheumatologyadvisor.com/home/topics/osteoarthritis/fda-to-review-tanezumab-a-potential-first-in-class-treatment-for-osteoarthritis-pain/

Park, M. (2010, February 2). Medical journal retracts study linking autism to vaccine. CNN Health. Retrieved from http://www.cnn.com/2010/HEALTH/02/02/lancet.retraction.autism/index.html

Park, M. (2012, September 5). Using chemical castration to punish child sex crimes. CNN Health. Retrieved from http://www.cnn.com/2012/09/05/health/chemical-castration-science/

Parker, E. S., Cahill, L., & McGaugh, J. L. (2006). A case of unusual autobiographical remembering. Neurocase, 12, 35–49.

Parker, S. E., Mai, C. T., Canfield, M. A., Rickard, R., Wang, Y., Meyer, R. E., et al. (2010). Updated national birth prevalence estimates for selected birth defects in the United States, 2004–2006. Birth Defects Research A: Clinical and Molecular Teratology, 88, 1008–1016.

Pascual-Leone, A., & Torres, F. (1993). Plasticity of the sensorimotor cortex representation of the reading finger in Braille readers. Brain, 116, 39–52.

Passamonti, L., Crockett, M. J., Apergis-Schoute, A. M., Clark, L., Rowe, J. B., Calder, A. J., & Robins, T. W. (2012). Effects of acute tryptophan depletion on prefrontal-amygdala connectivity while viewing facial signals of aggression. Biological Psychiatry, 71, 36–43.

Pastalkova, E., Itskov, V., Amarasingham, A., & Buzsáki, G. (2008). Internally generated cell assembly sequences in the rat hippocampus. Science, 321, 1322–1327.

Patel, A. B., Loerwald, K. W., Huber, K. M., & Gibson, J. R. (2014). Postsynaptic FMRP promotes the pruning of cell-to-cell connections among pyramidal neurons in the L5A neocortical network. Journal of Neuroscience, 34, 3413–3418.

Patel, A. J., Honoré, E., Lesage, F., Fink, M., Romey, G., & Lazdunski, M. (1999). Inhalational anesthetics activate two-pore-domain background K+ channels. Nature Neuroscience, 2, 422–426.

Paterson, R. W., Slattery, C. F., Poole, T., Nicholas, J. M., Magdalinou, N. K., Toombs, J., et al. (2018). Cerebrospinal fluid in the differential diagnosis of Alzheimer’s disease: Clinical utility of

an extended panel of biomarkers in a specialist cognitive clinic. Alzheimer's Research & Therapy, 10, Article 32. Retrieved from https://alzres.biomedcentral.com/articles/10.1186/s13195-018-0361-3

Paulesu, E., Danelli, L., & Berlingeri, M. (2014). Reading the dyslexic brain: Multiple dysfunctional routes revealed by a new meta-analysis of PET and fMRI activation studies. Frontiers in Human Neuroscience, 8, 830. Retrieved from https://doi.org/10.3389/fnhum.2014.00830

Paulesu, E., Démonet, J. F., Fazio, F., McCrory, E., Chanoine, V., Brunswick, N., et al. (2001). Dyslexia: Cultural diversity and biological unity. Science, 291, 2165–2167.

Pavăl, D. (2017). A dopamine hypothesis of autism spectrum disorder. Developmental Neuroscience, 39, 355–360.

Pavlopoulos, E., Jones, S., Kosmidis, S., Close, M., Kim, C., Kovalerchik, O., et al. (2013). Molecular mechanism for age-related memory loss: The histone-binding protein RbAp48. Science Translational Medicine, 5, 200ra115. Retrieved from http://stm.sciencemag.org/content/5/200/200ra115

Pearlman, A. (2017, November 16). Biohackers are using CRISPR on their DNA and we can't stop it. New Scientist. Retrieved from https://www.newscientist.com/article/mg23631520-100-biohackers-are-using-crispr-on-their-dna-and-we-cant-stop-it

Pearlson, G. D., Kim, W. S., Kubos, K. L., Moberg, P. J., Jayaram, G., Bascom, M. J., et al. (1989). Ventricle-brain ratio, computed tomographic density, and brain area in 50 schizophrenics. Archives of General Psychiatry, 46, 690–697.

Pedersen, N. W., Holm, A., Kristensen, N. P., Bjerregaard, A.-M., Bentzen, A. K., Marquard, A. M., et al. (2019). CD8+ T cells from

patients with narcolepsy and healthy controls recognize hypocretin neuron-specific antigens. Nature Communications, 10, 837. Retrieved from https://doi.org/10.1038/s41467-019-08774-1

Peeters, R., Simone, L., Nelissen, K., Fabbri-Destro, M., Vanduffel, W., Rizzolatti, G., et al. (2009). The representation of tool use in humans and monkeys: Common and uniquely human features. Journal of Neuroscience, 29, 11523–11539.

Pellegrino, L. J., Pellegrino, A. S., & Cushman, A. J. (1979). A stereotaxic atlas of the rat brain (2nd ed.). New York, NY: Plenum Press.

Penfield, W. (1955). The permanent record of the stream of consciousness. Acta Psychologica, 11, 47–69.

Penfield, W. (1958). The excitable cortex in conscious man. Springfield, IL: Charles C Thomas.

Penfield, W., & Rasmussen, T. (1950). The cerebral cortex of man. New York, NY: Macmillan.

Penke, L., Maniega, S. M., Bastin, M. E., Hernández, M. C. V., Murray, C., Royle, N. A., et al. (2012). Brain white matter tract integrity as a neural foundation for general intelligence. Molecular Psychiatry, 17, 1026–1030.

Pennacchio, L. A., Ahituv, N., Moses, A. M., Prabhakar, S., Nobrega, M. A., Shoukry, M., et al. (2006). *In vivo* enhancer analysis of human conserved non-coding sequences. Nature, 444, 499–502.

Pentel, P. R., Malin, D. H., Ennifar, S., Hieda, Y., Keyler, D. E., Lake, J. R., et al. (2000). A nicotine conjugate vaccine reduces nicotine distribution to brain and attenuates its behavioral and

cardiovascular effects in rats. Pharmacology, Biochemistry, and Behavior, 65, 191–198.

Pepperberg, I. M. (1993). Cognition and communication in an African grey parrot (*Psittacus erithacus*): Studies on a nonhuman, nonprimate, nonmammalian subject. In H. L. Roitblat, L. M. Herman, & P. E. Nachtigall (Eds.), Language and communication: Comparative perspectives (pp. 221–248). Hillsdale, NJ: Lawrence Erlbaum.

Percy, Z., Xu, Y., Sucharew, H., Khoury, J. C., Calafat, A. M., Braun, J. M., et al. (2016). Gestational exposure to phtalates and gender-related play behaviors in 8-year-old children: An observational study. Environmental Health, 15, 87. Retrieved from https://ehjournal.biomedcentral.com/articles/10.1186/s12940-016-0171-7

Perkel, D. J., & Farries, M. A. (2000). Complementary “bottom-up” and “top-down” approaches to basal ganglia function. Current Opinion in Neurobiology, 10, 725–731.

Perkins, A., & Fitzgerald, J. A. (1992). Luteinizing hormone, testosterone, and behavioral response of male-oriented rams to estrous ewes and rams. Journal of Animal Science, 70, 1787–1794.

Perlis, M. L., Smith, M. T., Andrews, P. J., Orff, H., & Giles, D. E. (2001). Beta/gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. Sleep, 24, 110–117.

Perrin, J. S., Merz, S., Bennett, D. M., Currie, J., Steele, D. J., Reid, I. C., & Schwarzbauer, C. (2012). Electroconvulsive therapy reduces frontal cortical connectivity in severe depressive disorder. Proceedings of the National Academy of Sciences, 109, 5464–5468.

Perrin, J. S., Leonard, G., Perron, M., Pike, G. B., & Pitiot, A. (2009). Sex differences in the growth of white matter during adolescence. NeuroImage, 45, 1055–1066.

Persson, J., Herlitz, A., Engman, J., Morell, A., Sjölie, D., Wikström, J., et al. (2013). Remembering our origin: Gender differences in spatial memory are reflected in gender differences in hippocampal lateralization. Behavioural Brain Research, X, 219–228.

Pert, C. B., & Snyder, S. H. (1973). Opiate receptor: Demonstration in nervous tissue. Science, 179, 1011–1014.

Petersen, M. R., Beecher, M. D., Zoloth, S. R., Moody, D. B., & Stebbins, W. C. (1978). Neural lateralization of species-specific vocalizations by Japanese macaques (*Macaca fuscata*). Science, 202, 324–326.

Petersen, S. E., Fox, P. T., Snyder, A. Z., & Raichle, M. E. (1990). Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli. Science, 249, 1041–1044.

Peterson, B. S., Skudlarski, P., Gatenby, J. C., Zhang, H., Anderson, A. W., & Gore, J. C. (1999). An fMRI study of Stroop word-color interference: Evidence for cingulate subregions subserving multiple distributed attentional systems. Biological Psychiatry, 45, 1237–1258.

Peterson, B. S., Warner, V., Bansal, R., Zhu, H., Hao, X., Liu, J., et al. (2009). Cortical thinning in persons at increased familial risk for major depression. Proceedings of the National Academy of Sciences, 106, 6273–6278.

Petit, D., Pennestri, M.-H., Pacquet, J., Desautels, A., Zadra, A., Vitaro, F., et al. (2015). Childhood sleepwalking and sleep terrors: A longitudinal study of prevalence and familial aggregation. JAMA Pediatrics, 169, 653–658.

Petitto, L. A., Holowka, S., Sergio, L. E., & Ostry, D. (2001). Language rhythms in baby hand movements. Nature, 413, 35–36.

Petitto, L. A., & Marentette, P. F. (1991). Babbling in the manual mode: Evidence for the ontogeny of language. Science, 251, 1493–1496.

Petitto, L. A., Zatorre, R. J., Gauna, K., Nikelski, E. J., Dostie, D., & Evans, A. C. (2000). Speech-like cerebral activity in profoundly deaf people processing signed languages: Implications for the neural basis of human language. Proceedings of the National Academy of Sciences, 97, 13961–13966.

Petrovic, P. (2005). Opioid and placebo analgesia share the same network. *Seminars in Pain and Medicine*, 3, 31–36.

Petrovic, P., Kalso, E., Petersson, K. M., & Ingvar, M. (2002). Opioid and placebo analgesia: Imaging a shared neuronal network. Science, 295, 1737–1740.

Petrulis, A., & Johnston, R. E. (1999). Lesions centered on the medial amygdala impair scent-marking and sex-odor recognition but spare discrimination of individual odors in female golden hamsters. Behavioral Neuroscience, 113, 345–357.

Peuskens, H., Sunaert, S., Dupont, P., Van Hecke, P., & Orban, G. A. (2001). Human brain regions involved in heading estimation. Journal of Neuroscience, 21, 2451–2461.

Pew Research Center. (2006, February 21). Supreme Court rules that religious group can use illegal drug in their worship services. Retrieved from http://www.pewforum.org/2006/02/21/supreme-court-rules-that-religious-group-can-use-illegal-drug-in-their-worship-services

Pfaus, J. G., Kleopoulos, S. P., Mobbs, C. V., Gibbs, R. B., & Pfaff, D. W. (1993). Sexual stimulation activates c-fos within estrogen-concentrating regions of the female rat forebrain. Brain Research, 624, 253–267.

Pfrieger, F. W., & Barres, B. A. (1997). Synaptic efficacy enhanced by glial cells in vitro. Science, 277, 1684–1687.

Phillips, A. G., Coury, A., Fiorino, D., LePiane, F. G., Brown, E., & Fibiger, H. C. (1992). Self-stimulation of the ventral tegmental area enhances dopamine release in the nucleus accumbens. Annals of the New York Academy of Sciences, 654, 199–206.

Phillips, R. J., & Powley, T. L. (1996). Gastric volume rather than nutrient content inhibits food intake. American Journal of Regulatory, Integrative, and Comparative Physiology, 271, R766–R779.

Picciotto, M. R. (2013). Nicotine, food intake, and activation of POMC neurons. Neuropsychopharmacology, 38, 245.

Pickar, D. (1995). Prospects for pharmacotherapy of schizophrenia. Lancet, 345, 557–562.

Pickens, C. L., Theberge, A. M., Fanous, S., Hope, B. T., & Shaham, Y. (2011). Neurobiology of the incubation of drug craving. Trends in Neurosciences, 34, 411–420.

Pietiläinen, K. H., Kaprio, J., Borg, P., Plasqui, G., Yki-Järvinen, H., Kujala, U. M., et al. (2008). Physical inactivity and obesity: A vicious circle. Obesity, 16, 409–414.

Pietschnig, J., Penke, L., Wicherts, J. M., Zeiler, M., & Voracek, M. (2015). Meta-analysis of associations between human brain volume and intelligence differences: How strong are they and what

do they mean? Neuroscience and Biobehavioral Reviews, 57, 411–432.

Pihl, R. O., & Peterson, J. B. (1993). Alcohol, serotonin, and aggression. Alcohol Health and Research World, 17, 113–116.

Pillay, P., & Manger, P. R. (2007). Order-specific quantitative patterns of cortical gyrification. European Journal of Neuroscience, 25, 2705–2712.

Pilowsky, L. S., Costa, D. C., Eli, P. J., Murray, R. M., Verhoeff, N. P., & Kerwin, R. W. (1993). Antipsychotic medication, D2 dopamine receptor blockade and clinical response: A 123I-IBZM SPET (single photon emission tomography) study. Psychological Medicine, 23, 791–799.

Pinker, S. (1994). The language instinct. New York, NY: Morrow.

Pinker, S. (2001). Talk of genetics and vice versa. Nature, 413, 465–466.

Pinyon, J. L., Tadros, S. F., Froud, K. E., Wong, A. C. Y., Tompson, I. T., Crawford, E. N., et al. (2014). Close-field electroporation gene delivery using the cochlear implant electrode array enhances the bionic ear. Science Translational Medicine, 6(233), 233ra54.

Pi-Sunyer, X. (2003). A clinical view of the obesity problem. Science, 299, 859–860.

Pi-Sunyer, X., Kissileff, H. R., Thornton, J., & Smith, G. P. (1982). C terminal octapeptide of cholecystokinin decreases food intake in obese men. Physiology and Behavior, 29, 627–630.

Platje, E., Popma, A., Vermeiren, R. R. J. M., Doreleijers, T. A. H., Meeus, W. H. J., van Lier, P. A. C., et al. (2015). Testosterone and cortisol in relation to aggression in a non-clinical sample of boys and girls. Aggressive Behavior, 41, 478–487.

Plomin, R. (1990). The role of inheritance in behavior. Science, 248, 183–188.

Plomin, R., & McClearn, G. E. (Eds.). (1993). Nature, nurture, and psychology. Washington, DC: American Psychological Association.

Plomin, R., Owen, M. J., & McGuffin, P. (1994). The genetic basis of complex human behaviors. Science, 264, 1733–1739.

Plomin, R., & von Stumm, S. (2018). The new genetics of intelligence. Nature Reviews Genetics, 19(3), 148–159.

Plotnik, J. M., de Waal, F. B. M., & Reiss, D. (2006). Self recognition in an Asian elephant. Proceedings of the National Academy of Sciences, 103, 17053–17057.

Poggio, G. F., & Poggio, T. (1984). The analysis of stereopsis. Annual Review of Neuroscience, 7, 379–412.

Poirer, C., Boumans, T., Verhoye, M., Balthazart, J., & Van der Linden, A. (2009). Own-song recognition in the songbird auditory pathway: selectivity and lateralization. Journal of Neuroscience, 29, 2252–2258.

Polderman, T. J. C., Kreukels, B. P. C., Irwig, M. S., Beach, L., Chan, Y.-M., Derks, E. M., et al. (2018). The biological contributions to gender identity and gender diversity: Bringing data to the table. Behavior Genetics, 48, 95–108.

Popova, S., Lange, S., Probst, C., Gmel, G., & Rehm, J. (2017). Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: A systematic review and meta-analysis. Lancet Global Health, 5, e290–e299. doi:10.1016/S2214-109X(17)30021-9

Porter, J., Craven, B., Khan, R. M., Chang, S.-J., Kang, I., Judkewicz, B., et al. (2007). Mechanisms of scent-tracking in humans. Nature Neuroscience, 10, 27–29.

Porto, P. R., Oliveira, L., Mari, J., Volchan, E., Figueira, I., & Ventura, P. (2009). Does cognitive therapy change the brain? A systematic review of neuroimaging in anxiety disorders. Journal of Neuropsychiatry and Clinical Neuroscience, 21, 114–125.

Posthuma, D., De Geus, E. J., & Boomsma, D. I. (2001). Perceptual speed and IQ are associated through common genetic factors. Behavior Genetics, 31, 593–602.

Potter, W. Z., & Rudorfer, M. V. (1993). Electroconvulsive therapy: A modern medical procedure. New England Journal of Medicine, 328, 882–883.

Pournaras, D. J., & le Roux, C. W. (2009). Obesity, gut hormones, and bariatric surgery. World Journal of Surgery, 33, 1983–1988.

Power, R. A., Steinberg, S., Bjornsdottir, G., Rietveld, C. A., Abdellaoui, A., Nivard, M. M., et al. (2015). Polygenic risk scores for schizophrenia and bipolar disorder predict creativity. Nature Neuroscience, 18, 953–955.

Powers, J. (2010, July 9). Gender issue finally resolved. Boston Globe. Retrieved from http://www.boston.com/sports/other_sports/olympics/articles/2010/07/09/gender_issue_finally_resolved

Prabhakar, S., Visel, Z., Akiyama, J. A., Shoukry, M., Lewis, K. D., Holt, A., et al. (2008). Human-specific gain of function in a developmental enhancer. Science, 321, 1346–1350.

Prather, J. F., Peters, S., Nowicki, S., & Mooney, R. (2008). Precise auditory-vocal mirroring in neurons for learned vocal communication. Nature, 415, 305–310.

Prehn-Kristensen, A., Munz, M., Göder, R., Wilhelm, I., Korr, K., Vahl, W., et al. (2014). Transcranial oscillatory direct current stimulation during sleep improves declarative memory consolidation in children with attention-deficit/hyperactivity disorder to a level comparable to healthy controls. Brain Stimulation, 7, 793–799.

Preston, J. D., O'Neal, J. H., & Talaga, M. C. (2017). Handbook of clinical psychopharmacology for therapists (8th ed.). Oakland CA: New Harbinger Publications.

Preston, S. H., Vierboom, Y. C., & Stokes, A. (2018). The role of obesity in exceptionally slow US mortality improvement. Proceedings of the National Academy of Sciences USA, 115, 957–961.

Price, D. D. (2000). Psychological and neural mechanisms of the affective dimension of pain. Science, 288, 1769–1772.

Price, J. (1968). The genetics of depressive behavior. British Journal of Psychiatry (Special Publication No. 2), 37–45.

Price, R. A., Kidd, K. K., Cohen, D. J., Pauls, D. L., & Leckman, J. F. (1985). A twin study of Tourette syndrome. Archives of General Psychiatry, 42, 815–820.

Prior, H., Schwarz, A., & Güntürkün, O. (2008). Mirror-induced behavior in the magpie (*Pica pica*): Evidence of self-recognition. PLoS Biology, 6(8), e202. Retrieved from http://www.plosbiology.org/article/info:doi/10.1371/journal.pbio.0060202

Proal, E., Reiss, P. T., Klein, R. G., Mannuzza, S., Gotimer, K., Ramos-Olazagasti, M. A., et al. (2011). Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood. Archives of General Psychiatry, 68, 1122–1134.

Proof? The joke was on Bischoff, but too late. (1942, March). Scientific American, 166(3), 145.

Prospective Studies Collaboration. (2009). Body-mass index and cause-specific mortality in 900 000 adults: Collaborative analyses of 57 prospective studies. Lancet, 373, 1083–1096.

Prufer, K., Munch, K., Hellmann, I., Akagi, K., Miller, J. R., Walenz, B., et al. (2012). The bonobo genome compared with the chimpanzee and human genomes. Nature, 486(7404), 527–531.

Prusiner, S. B. (n.d.). Stanley B. Prusiner quotes. BrainyQuote.com. Retrieved from https://www.brainyquote.com/quotes/stanley_b_prusiner_639569

Purves, D., Augustine, G. J., Fitzpatrick, D., Hall, W. C., LaMantia, A.-S., Mooney, R. D., et al. (2018). Neuroscience (6th ed.). New York, NY: Oxford University Press.

Puts, D. A., McDaniel, M. A., Jordan, C. L., & Breedlove, S. M. (2008). Spatial ability and prenatal androgens: Meta-analyses of congenital adrenal hyperplasia and digit ratio (2D:4D) studies. Archives of Sexual Behavior, 37(1), 100–111.

Pyter, L. M., Pineros, V., Galang, J. A., McClintock, M. K., & Prendergast, B. J. (2009). Peripheral tumors induce depressive-like behaviors and cytokine production and alter hypothalamic-pituitary-adrenal axis regulation. Proceedings of the National Academy of Sciences, 106, 9069–9074.

Qadri, Y. J., Bortsov, A. V., Swor, R. A., Peak, D. A., Jones, J. S., Rathlev, N. K., et al. (2012). Genetic polymorphisms in the dopamine receptor D2 are associated with acute pain severity after motor vehicle collision. Paper presented at the annual meeting of the American Society of Anesthesiologists, October 16, Washington, DC.

Qin, B., Plassman, B. L., Edwards, L. J., Popkin, B. M., Adair, L. S., & Mendez, M. A. (2014). Fish intake is associated with slower cognitive decline in Chinese older adults. Journal of Nutrition, 144, 1579–1585.

Qin, Y.-L., McNaughton, B. L., Skaggs, W. E., & Barnes, C. A. (1997). Memory reprocessing in corticocortical and hippocampocortical neuronal ensembles. Philosophical Transactions of the Royal Society of London, B, 352, 1525–1533.

Qiu, X., Kumbalasiri, T., Carlson, S. M., Wong, K. Y., Krishna, V., Provencio, I., et al. (2005). Induction of photosensitivity by heterologous expression of melanopsin. Nature, 433, 745–749.

Quian Quiroga, R., Kraskov, A., Koch, C., & Fried, I. (2009). Explicit encoding of multimodal percepts by single neurons in the human brain. Current Biology, 19(15), 1308–1313.

Quian Quiroga, R., Kraskov, A., Mormann, F., Fried, I., & Koch, C. K. (2014). Single-cell responses to face adaptation in the human medial temporal lobe. Neuron, 84, 363–369.

Rabl, U., Meyer, B. M., Diers, K., Bartova, L., Berger, A., Mandorfer, D., et al. (2014). Additive gene-environment effects on hippocampal structure in healthy humans. Journal of Neuroscience, 34, 9917–9926.

Raboch, J., & Stárka, L. (1973). Reported coital activity of men and levels of plasma testosterone. Archives of Sexual Behavior, 2, 309–315.

Ragozzino, M. E. (2007). The contribution of the medial prefrontal cortex, orbitofrontal cortex, and dorsomedial striatum to behavioral flexibility. Annals of the New York Academy of Sciences, 1121, 355–375.

Ragsdale, D. S., McPhee, J. C., Scheuer, T., & Catterall, W. A. (1994). Molecular determinants of state-dependent block of Na+ channels by local anesthetics. Science, 265, 1724–1728.

Rahman, Q., Abrahams, S., & Wilson, G. D. (2003). Sexual-orientation-related differences in verbal fluency. Neuropsychology, 17, 240–246.

Raine, A. (2013, April 26). The criminal mind. Wall Street Journal. Retrieved from http://online.wsj.com/article/SB10001424127887323335404578444682892520530.html

Raine, A., Meloy, J. R., Bihrle, S., Stoddard, J., LaCasse, L., & Buchsbaum, M. S. (1998). Reduced prefrontal and increased subcortical brain functioning assessed using positron emission tomography in predatory and affective murderers. Behavioral Science and Law, 16, 319–332.

Raine, A., Yang, Y., Narr, K. L., & Toga, A. W. (2009, December 22). Sex differences in orbitofrontal gray as a partial explanation for

sex differences in antisocial personality. Molecular Psychiatry. doi:10.1038/mp.2009.136

Rainer, G. S., Rao, S. C., & Miller, E. K. (1999). Prospective coding for objects in primate prefrontal cortex. Journal of Neuroscience, 19, 5493–5505.

Rainville, P., Duncan, G. H., Price, D. D., Carrier, B., & Bushnell, M. C. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science, 227, 968–971.

Raja, S. N., Meyer, R. A., Ringkamp, M., & Campbell, J. N. (1999). Peripheral neural mechanisms of nociception. In P. D. Wall & R. Melzack (Eds.), Textbook of pain (pp. 11–57). Edinburgh, Scotland: Churchill Livingstone.

Rajendran, L., & Paolicelli, R. C. (2018). Microglia-mediated synapse loss in Alzheimer's disease. Journal of Neuroscience, 38, 2911–2919.

Rakic, P. (1985). Limits of neurogenesis in primates. Science, 227, 1054–1056.

Ramachandran, V. S., & Altschuler, E. L. (2009). The use of visual feedback, in particular mirror visual feedback, in restoring brain function. Brain, 132, 1693–1710.

Ramachandran, V. S., & Blakeslee, S. (1998). Phantoms in the brain. New York, NY: Morrow.

Ramey, C. T., Campbell, F. A., Burchinal, M., Skinner, M. L., Gardner, D. M., & Ramey, S. L. (2000). Persistent effects of early childhood education on high-risk children and their mothers. Applied Developmental Science, 4, 2–14.

Ramón y Cajal, S. (1989). Recollections of my life (E. H. Craigie & J. Cano, Trans.). Cambridge, MA: MIT Press. (Original work published 1937)

Ramsay, G., & Martin, J. (2020). Caster Semenya loses appeal in Swiss court over restriction of testotsterone levels. CNN. Retrieved from https://edition.cnn.com/2020/09/09/sport/caster-semenya-ruling-athletics-spt-intl/index.html

Ramus, F., Rosen, S., Dakin, S. C., Day, B. L., Castellote, J. M., White, S., et al. (2003). Theories of developmental dyslexia: Insights from a multiple case study of dyslexic adults. Brain, 126, 841–865.

Rao, A. N., Falnikar, A., O'Toole, E. T., Morphew, M. K., Hoenger, A.., Davidson, M. W. et al. (2016). Sliding of centrosome-unattached microtubules defines key features of neuronal phenotype. Journal of Cell Biology, 213, 329-341.

Rao, S. C., Rainer, G., & Miller, E. K. (1997). Integration of what and where in the primate prefrontal cortex. Science, 276, 821–824.

Rapoport, J. L. (1991). Recent advances in obsessive-compulsive disorder. Neuropsychopharmacology, 5, 1–10.

Rasmussen, T., & Milner, B. (1977). The role of early left-brain injury in determining lateralization of cerebral speech functions. Annals of the New York Academy of Sciences, 299, 355–369.

Ratliff, C. P., Borghuis, B. G., Kao, Y.-H., Sterling, P., & Balasubramanian, V. (2010). Retina is structured to process an excess of darkness in natural scenes. Proceedings of the National Academy of Sciences, 107, 17368–17373.

Ratliff, F., & Hartline, H. K. (1959). The responses of Limulus optic nerve fibers to patterns of illumination on the receptor mosaic. Journal of General Physiology, 42, 1241–1255.

Rauch, V., Arunajadai, S., Horton, M., Perera, F., Hoepner, L., Barr, D. B., & Whyatt, R. (2011). Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. Environmental Health Perspectives, 119, 1196–1201.

Rauschecker, J. P., & Tian, B. (2000). Mechanisms and streams for processing of “what” and “where” in auditory cortex. Proceedings of the National Academy of Sciences, 97, 11800–11806.

Ravelli, G. P., Stein, Z. A., & Susser, M. W. (1976). Obesity in young men after famine exposure in utero and early infancy. New England Journal of Medicine, 295, 349–353.

Raven, J. C. (2003). Standard progressive matrices (manual). San Antonio, TX: PsychCorp/Pearson.

Ray, L. A., & Hutchison, K. E. (2004). A polymorphism of the μ-opioid receptor gene (*OPRM1*) and sensitivity to the effects of alcohol in humans. Alcoholism Clinical and Experimental Research, 28, 1789–1795.

Ray, R. A., Bujarski, S., MacKillop, J., Courtney, K. E., Monti, P. M., & Miotto, K. (2012). Subjective response to alcohol among alcohol-dependent individuals: Effects of the mu-opioid receptor (OPRM1) gene and alcoholism severity. Alcoholism: Clinical & Experimental Research, 37, E116–E124.

Ray, W. J. (2014). Abnormal Psychology. Thousand Oaks, CA: Sage.

Reber, P. (2010, May 1). What is the memory capacity of the human brain? Scientific American Mind. Retrieved from https://www.scientificamerican.com/article/what-is-the-memory-capacity

Recht, L. D., Lew, R. A., & Schwartz, W. J. (1995). Baseball teams beaten by jet lag. Nature, 377, 583.

Reddihough, D., Marraffa, C., Mouti, A., O'Sullivan, M., Lee, K. J., Orsini, F., et al. (2019). A randomised placebo-controlled trial to determine if fluoxetine is effective for improving autistic behaviors. Journal of Paediatrics and Child Health, 55(Suppl 2), 8–9.

Redelmeier, D. A., & Tibshirani, R. J. (1997). Association between cellular telephone calls and motor vehicle collisions. New England Journal of Medicine, 336, 453–458.

Redinbaugh, M. J., Phillips, J. M., Kambi, N. A., Mohanta, S., Andryk, S., Dooley, G. L., et al. (2020). Thalamus modulates consciousness via layer-specific control of cortex. Neuron, 106, 66–75.

Reed, J. J., & Squire, L. R. (1998). Retrograde amnesia for facts and events: Findings from four new cases. Journal of Neuroscience, 18, 3943–3954.

Reed, T. E., & Jensen, A. R. (1992). Conduction velocity in a brain nerve pathway of normal adults correlates with intelligence level. Intelligence, 16, 259–272.

Regalado, A. (2019, February 21). China's CRISPR twins might have had their brains inadvertently enhanced. MIT Technology Review. Retrieved from https://www.technologyreview.com/s/612997/the-crispr-twins-had-their-brains-altered

Reichenberg, A., Caspi, A., Harrington, H., Houts, R., Keefe, R. S. E., Murray, R. M., et al. (2010). Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: A 30-year study. American Journal of Psychiatry, 167, 160–169.

Reichmann, F., & Holzer, P. (2016). Neuropeptide Y: A stressful review. Neuropeptides, 55, 99–109.

Reilly, D., Neumann, D. L., & Andrews, G. (2015). Sex differences in mathematics and science achievement: A meta-analysis of National Assessment of Educational Progress assessments. Journal of Educational Psychology, 107, 645–662.

Reilly, D., Neumann, D. L., & Andrews, G. (2017). Gender differences in spatial ability: Implications for STEM education and approaches to reducing the gender gap for parents and educators. In M. S. Khine (Ed.), Visual-spatial ability in STEM education: Transforming research into practice (pp. 195–224). Cham, Switzerland: Springer International.

Reiman, E. M., Armstrong, S. M., Matt, K. S., & Mattox, J. H. (1996). The application of positron emission tomography to the study of the normal menstrual cycle. Human Reproduction, 11, 2799–2805.

Reinders, A. A. T. S., Chalavi, S., Schlumpf, Y. R., Vissia, E. M., Nijenhuis, E. R. S., Jäncke, L, & Ecker, C. (2018). Neurodevelopmental origins of abnormal cortical morphology in dissociative identity disorder. Acta Psychiatrica Scandinavica, 137, 157–170.

Reinders, A. A. T. S., Marquand, A. F., Schlumpf, Y. R., Chalavi, S., Vissia, E. M., Nijenhuis, E. R. S., & Veltman, D. J. (2019). Aiding the diagnosis of dissociative identity disorder: Pattern recognition study of brain biomarkers. British Journal of Psychiatry, 215, 536–544.

Reinders, A. A. T. S., Nijenhuis, E. R., Quak, J., Korf, J., Haaksma, J., Paans, A. M., et al. (2006). Psychobiological characteristics of dissociative identity disorder: A symptom provocation study. Biological Psychiatry, 60, 730–740.

Reiner, W. G., & Gearhart, J. P. (2004). Discordant sexual identity in some genetic males with cloacal exstrophy assigned to female sex at birth. New England Journal of Medicine, 350, 333–341.

Reininghaus, U., Gayer-Anderson, C., Valmaggia, L., Kempton, M. J., Calem, M., Onyejiaka, A., et al. (2016). Psychological processes underlying the association between childhood trauma and psychosis in daily life: An experience sampling study. Psychological Medicine, 46, 2799–2813.

Reinisch, J. M. (1981). Prenatal exposure to synthetic progestins increases potential for aggression in humans. Science, 211, 1171–1173.

Reisberg, B., Doody, R., Stöffler, A., Schmitt, F., Ferris, S., & Möbius, H. J. (2003). Memantine in moderate-to-severe Alzheimer's disease. New England Journal of Medicine, 348, 1333–1341.

Reiss, D., & Marino, L. (2001). Mirror self-recognition in the bottlenose dolphin: A case of cognitive convergence. Proceedings of the National Academy of Sciences, 98, 5937–5942.

Rempel-Clower, N. L., Zola, S. M., Squire, L. R., & Amaral, D. G. (1996). Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. Journal of Neuroscience, 16, 5233–5255.

Renault, B., Signoret, J.-L., Debruille, B., Breton, F., & Bolger, F. (1989). Brain potentials reveal covert facial recognition in prosopagnosia. Neuropsychologia, 27, 905–912.

Renier, L. A., Anurova, I., De Volder, A. G., Carlson, S., VanMeter, J., & Rauschecker, J. P. (2010). Preserved functional specialization for spatial processing in the middle occipital gyrus of the early blind. Cell, 68, 138–148.

RetroSense Therapeutics completes low dose cohort in clinical trial of novel gene therapy application of optogenetics. (2016, August 10). BusinessWire. Retrieved from https://www.businesswire.com/news/home/20160810005731/en/RetroSense-Therapeutics-Completes-Dose-Cohort-Clinical-Trial

Rezaii, N., Walker, E., & Wolff, P. (2019). A machine learning approach to predicting psychosis using semantic density and latent content analysis. NPJ Schizophrenia, 5, e9.

Ribary, U. (2005). Dynamics of thalamo-cortical network oscillations and human perception. In S. LaurefKraeys (Ed.), The boundaries of consciousness: Neurobiology and neuropathology (pp. 127–142). New York, NY: Elsevier.

Ribiez, S. R., Duran, F., Oliviera, M. C., Bezerra, D., Castro, C. C., Steffens, D. C., et al. (2013). Structural brain changes as biomarkers and outcome predictors in patients with late-life depression: A cross-sectional and prospective study. PLoS One, 8(11), e80049.

Rice, F., Harold, G. T., Bolvin, J., Hay, D. F., van den Bree, M., & Thapar, A. (2009). Disentangling prenatal and inherited influences in humans with an experimental design. Proceedings of the National Academy of Sciences, 106, 2464–2467.

Rice, M. L., Smith, S. D., & Gayán, J. (2009). Convergent genetic linkage and associations to language, speech and reading measures in families of probands with specific language impairment. Journal of Neurodevelopmental Disorders, 1, 264–282.

Rice, W. R., Friberg, U., & Gavrilets, S. (2012). Homosexuality as a consequence of epigenetically canalized sexual development. Quarterly Review of Biology, 87, 343–368.

Richardson, C., Glenn, S., Nurmikko, T., & Horgan, M. (2006). Incidence of phantom phenomena including phantom limb pain 6 months after major lower limb amputation in patients with peripheral vascular disease. Clinical Journal of Pain, 22, 353–358.

Ridaura, V. K., Faith, J. J., Rey, F. E., Cheng, J., Duncan, A. E., Kau, A. L., et al. (2013). Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science, 341, 6150. Retrieved from http://www.sciencemag.org/content/341/6150/1241214.abstract

Riedel, G., Micheau, J., Lam, A. G. M., Roloff, E. V. L., Martin, S. J., Bridge, H., et al. (1999). Reversible neural inactivation reveals hippocampal participation in several memory processes. Nature Neuroscience, 2, 898–905.

Rieger, G., Linsenmeier, J. A. W., Gygax, L., & Bailey, J. M. (2008). Sexual orientation and childhood gender nonconformity: Evidence from home videos. Developmental Psychology, 44, 46–58.

Riehle, A., & Requin, J. (1989). Monkey primary motor and premotor cortex: Single-cell activity related to prior information about direction and extent of an intended movement. Journal of Neurophysiology, 61, 534–549.

Rijlaarsdam, J., Cecil, C. A. M., Walton, E., Mesirow, M. S. C., Relton, C. L., Gaunt, T. R., et al. (2017). Prenatal unhealthy diet, insulin-like growth factor 2 gene (*IGF2*) methylation, and attention deficit hyperactivity disorder symptoms in youth with early-onset conduct problems. Journal of Child Psychology and Psychiatry, 58, 19–27.

Rijo-Ferreira, F., & Takahashi, J. S. (2019). Genomics of circadian rhythms in health and disease. Genome Medicine, 11(1), 82. doi:10.1186/s13073-019-0704-0

Riley, K. P., Snowdon, D. A., Desrosiers, M. F., & Markesbery, W. R. (2005). Early life linguistic ability, late life cognitive function, and neuropathology: Findings from the nun study. Neurobiology of Aging, 26, 341–347.

Rimmele, U., Hediger, K., Heinrichs, M., & Klaver, P. (2009). Oxytocin makes a face in memory familiar. Journal of Neuroscience, 29, 38–42.

Risoud, M., Hanson, J.-N., Gauvrit, F., Renard, C., Lemesre, P.-E., Bonne, N.-X., & Vincent, C. (2018). Sound source localization. European Annals of Otorhinolaryngology, Head and Neck Diseases, 135, 259–264.

Ritchie, J. M., & Rogart, R. B. (1977). Density of sodium channels in mammalian myelinated nerve fibers and nature of the axonal membrane under the myelin sheath. Proceedings of the National Academy of Sciences, 74, 211–215.

Ritterband-Rosenbaum, A., Nielsen, J. B., & Christensen, M. S. (2014). Sense of agency is related to gamma band coupling in an inferior parietal-preSMA circuitry. Frontiers in Human Neuroscience, 16(8), 510. doi:10.3389/fnhum.2014.00510

Roberts, A. I., Vick, S.-J., Roberts, S. G. B., Buchanan-Smith, H. M., & Zuberbühler, K. (2012). A structure-based repertoire of manual gestures in wild chimpanzees: Statistical analyses of a graded communication system. Evolution and Human Behavior, 33, 578–589.

Robbins, T. W., & Clark, L. (2015). Behavioral addictions. Current Opinion in Neurobiology, 30, 66-72.

Robinson, T. E., Gorny, G., Mitton, E., & Kolb, B. (2001). Cocaine self-administration alters the morphology of dendrites and dendritic spines in the nucleus accumbens and neocortex. Synapse, 39, 257–266.

Robinson, T. E., & Kolb, B. (1997). Persistent structural modifications in nucleus accumbens and prefrontal cortex neurons produced by previous experience with amphetamine. Journal of Neuroscience, 17, 8491–8497.

Rodin, J., Schank, D., & Striegel-Moore, R. (1989). Psychological features of obesity. Medical Clinics of North America, 73, 47–66.

Rodriguez, A., & Bohlin, G. (2005). Are maternal smoking and stress during pregnancy related to ADHD symptoms in children? Journal of Child Psychology and Psychiatry, 46, 246–254.

Rodriguez, I. (2004). Pheromone receptors in mammals. Hormones and Behavior, 46, 219–230.

Rodriguez-Raecke, R., Niemeier, A., Ihle, K., Ruether, W., & May, A. (2009). Brain gray matter decrease in chronic pain is the consequence and not the cause of pain. Journal of Neuroscience, 29, 13746–13750.

Roe, A. W., Chelazzi, L., Connor, C. E., Conway, B. R., Fujita, I., Gallant, J. L., et al. (2012). Toward a unified theory of visual area V4. Neuron, 74, 12–29.

Roecklein, K. A., Rohan, K. J., Duncan, W. C., Rollag, M. D., Rosenthal, N. E., Lipsky, R. H., & Provencio, I. (2009). A missense variant (P10L) of the melanopsin (Opn4) gene is associated with Seasonal Affective Disorder. Journal of Affective Disorders, 114, 279–285.

Roecklein, K. A., Wong, P., Ernecoff, N., Miller, M., Donofry, S., Kamarck, M., et al. (2013). The post illumination pupil response is reduced in seasonal affective disorder. Psychiatry Research, 210, 150–158.

Roenneberg, T., Kuehnle, T., Pramstaller, P. P., Ricken, J., Havel, M., Guth, A., et al. (2004). A marker for the end of adolescence. Current Biology, 14, R1038–R1039.

Roffwarg, H. P., Muzio, J. N., & Dement, W. C. (1966). Ontogenetic development of the human sleep-dream cycle. Science, 152, 604–619.

Rogan, M. T., Stäubli, U. V., & LeDoux, J. E. (1997). Fear conditioning induces associative long-term potentiation in the amygdala. Nature, 390, 604–607.

Rolls, B. J., Rolls, E. T., Rowe, E. A., & Sweeney, K. (1981). Sensory-specific satiety in man. Physiology and Behavior, 27, 137–142.

Rolls, B. J., Rowe, E. A., & Turner, R. C. (1980). Persistent obesity in rats following a period of consumption of a mixed, high-energy diet. Journal of Physiology, 298, 415–427.

Rose, J. E., Brugge, J. F., Anderson, D. J., & Hind, J. E. (1967). Phase-locked response to low-frequency tones in single auditory nerve fibers of the squirrel monkey. Journal of Neurophysiology, 30, 769–793.

Rose, R. J. (1995). Genes and human behavior. Annual Review of Psychology, 46, 625–654.

Roselli, C. E., Larkin, K., Resko, J. A., Stellflug, J. N., & Stormshak, F. (2004). The volume of a sexually dimorphic nucleus in the ovine

medial preoptic area/anterior hypothalamus varies with sexual partner preference. Endocrinology, 145, 478–483.

Rosen, L. N., Targum, S. D., Terman, M., Bryant, M. J., Hoffman, H., Kasper, S. F., et al. (1990). Prevalence of seasonal affective disorder at four latitudes. Psychiatry Research, 31, 131–144.

Rosen, S. (1999). Most—but not all—regions see food gains. FoodReview, 22, 13–19.

Rosenberg, E., & Schweber, N. (2016, July 13). 33 suspected of overdosing on synthetic marijuana in Brooklyn. New York Times, p. A17.

Rosenthal, N. E., Sack, D. A., Carpenter, C. J., Parry, B. L., Mendelson, W. B., & Wehr, T. A. (1985). Antidepressant effects of light in seasonal affective disorder. American Journal of Psychiatry, 142, 163–170.

Rösler, A., & Witztum, E. (1998). Treatment of men with paraphilia with a long-acting analogue of gonadotropin-releasing hormone. New England Journal of Medicine, 338, 416–422.

Rösler, F., Heil, M., & Henninghausen, E. (1995). Distinct cortical activation patterns during long-term memory retrieval of verbal, spatial and color information. Journal of Cognitive Neuroscience, 7, 51–65.

Ross, G. W., Abbott, R. D., Petrivotch, H., Morens, D. M., Grandinetti, A., Tung, K.-H., et al. (2000). Association of coffee and caffeine intake with the risk of Parkinson disease. Journal of the American Medical Association, 283, 2674–2679.

Rothe, C., Gutknecht, L., Freitag, C., Tauber, R., Mössner, R., Franke, P., et al. (2004). Association of a functional 1019C>G 5-

HT1A receptor gene polymorphism with panic disorder with agoraphobia. International Journal of Neuropsychopharmacology, 7, 189–192.

Rothman, J. M., Van Soest, P. J., & Pell, A. N. (2006). Decaying wood is a sodium source for mountain gorillas. Biology Letters, 2, 321–324.

Rouw, R., & Scholte, S. (2007). Increased structural connectivity in grapheme-color synesthesia. Nature Neuroscience, 10, 792–797.

Rowe, M. L., & Goldin-Meadow, S. (2009). Differences in early gesture explain SES disparities in child vocabulary size at school entry. Science, 323, 951–953.

Rowland, L. P., Hoefer, P. F. A., & Aranow, H., Jr. (1960). Myasthenic syndromes. Research Publications—Association for Research in Nervous and Mental Disease, 38, 547–560.

Roy, A., DeJong, J., & Linnoila, M. (1989). Cerebrospinal fluid monoamine metabolites and suicidal behavior in depressed patients: A 5-year followup study. Archives of General Psychiatry, 46, 609–612.

Rozin, P. (1967). Specific aversions as a component of specific hungers. Journal of Comparative and Physiological Psychology, 64, 237–242.

Rozin, P. (1969). Adaptive food sampling patterns in vitamin deficient rats. Journal of Comparative and Physiological Psychology, 69, 126–132.

Rozin, P. (1976). The selection of foods by rats, humans, and other animals. Advances in the Study of Behavior, 6, 21–76.

Rubens, A. B. (1977). Anatomical asymmetries of human cerebral cortex. In S. Harnad, R. W. Doty, L. Goldstein, J. Jaynes, & G. Krauthamer (Eds.), Lateralization in the nervous system (pp. 503–516). New York, NY: Academic Press.

Rubino, F., Nathan, D. M., Eckel, R. H., Schauer, P. R., Alberti, K. G. M. M., Zimmet, P. Z., et al. (2016). Metabolic surgery in the treatment algorithm for Type 2 diabetes: A joint statement by international diabetes organizations. Diabetes Care, 39, 861–877.

Rudorfer, M. V., Henry, M. E., & Sackeim, H. A. (1997). Electroconvulsive therapy. In A. Tasman, J. Kay, & J. A. Lieberman (Eds.), Psychiatry (pp. 1535–1556). Philadelphia, PA: W. B. Saunders.

Rushton, J. P., & Jensen, A. R. (2005). Thirty years of research on race differences in cognitive ability. Psychology, Public Policy, and Law, 11, 235–294.

Rushton, W. A. H. (1951). A theory of the effects of fibre size in medullated nerve. Journal of Physiology, 115, 101–122.

Russell, S., Bennett, J., Wellman, J. A., Chung, D. C., Yu, Z.-F., Tillman, A., et al. (2017). Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: A randomised, controlled, open-label, phase 3 trial. Lancet, 390, 849–860.

Rutherford, W. (1886). The sense and hearing. Journal of Anatomy and Physiology, 21, 166–168.

Rutter, M. (1983). Cognitive deficits in the pathogenesis of autism. Journal of Child Psychology and Psychiatry, 24, 513–531.

Rutter, M. (2005). Incidence of autism spectrum disorders: Changes over time and their meaning. Acta Paediatrica, 94, 2–15.

Rutz, C., Klump, B. C., Komarczyk, L., Leighton, R., Kramer, J., Wischnewski, S., et al. (2016). Discovery of species-wide tool use in the Hawaiian crow. Nature, 537, 403–407.

Rylaarsdam, L., & Guemez-Gamboa, A. (2019). Genetic causes and modifiers of autism spectrum disorder. Frontiers in Cellular Neuroscience, 13, 385. Retrieved from https://www.frontiersin.org/articles/10.3389/fncel.2019.00385/full

Rzhetsky, A., Bagley, S. C., Wang, K., Lyttle, C. S., Cook, E. H., Jr., Altman, R. B., & Gibbons, R. D. (2014). Environmental and state-level regulatory factors affect the incidence of autism and intellectual disability. PLoS Computational Biology, 10, e1003518. Retrieved from http://www.ploscompbiol.org/article/info%3Adoi%2F10.1371%2Fjournal.pcbi.1003518

Saalmann, Y. B., Pigarev, I. N., & Vidyasagar, T. R. (2007). Neural mechanisms of visual attention: How top-down feedback highlights relevant locations. Science, 316, 1612–1615.

Saarimäki, H., Ejtehadian, L. F., Glerean, E., Jääskeläinen, I. P., Vuilleumier, P., Sams, M., & Nummenma, L. (2018). Distributed affective space repesents multiple emotion categories across the human brain. Social Cognitive and Affective Neuroscience, 13, 471–482.

Sabesan, R., Schmidt, B. P., Tuten, W. S., & Roorda, A. (2016). The elementary representation of spatial and color vision in the human retina. Science Advances, 2, e1600797.

Sacco, K. A., Termine, A., Seyal, A., Dudas, M. M., Vessicchio, J. C., Krishnan-Sarin, S., et al. (2005). Effects of cigarette smoking on

spatial working memory and attentional deficits in schizophrenia. Archives of General Psychiatry, 62, 649–659.

Sachs, B., & Meisel, R. L. (1994). The physiology of male sexual behavior. In J. D. Neill & E. Knobil (Eds.), The physiology of reproduction (Vol. 2, pp. 3–106). New York, NY: Raven Press.

Sack, A. T., Kohler, A., Bestmann, S., Linden, D. E. J., Dechent, P., Goebel, R., et al. (2007). Imaging the brain activity changes underlying impaired visuospatial judgments: Simultaneous fMRI, TMS, and behavioral studies. Cerebral Cortex, 17, 2841–2852.

Sack, D. A., Nurnberger, J., Rosenthal, N. E., Ashburn, E., & Wehr, T. A. (1985). Potentiation of antidepressant medications by phase advance of the sleep-wake cycle. American Journal of Psychiatry, 142, 606–608.

Sackeim, H. A., Luber, B., Katzman, G. P., Moeller, J. R., Prudic, J., Devanand, D. P., et al. (1996). The effects of electroconvulsive therapy on quantitative electroencephalograms: Relationship to clinical outcome. Archives of General Psychiatry, 53, 814–823.

Sackeim, H. A., Prohovnik, I., Moeller, J. R., Brown, R. P., Apter, S., Prudic, J., et al. (1990). Regional cerebral blood flow in mood disorders: I. Comparison of major depressives and normal controls at rest. Archives of General Psychiatry, 47, 60–70.

Sackeim, H. A., Prudic, J., Devanand, D. P., Kiersky, J. E., Fitzsimons, L., Moody, B. J., et al. (1993). Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. New England Journal of Medicine, 328, 839–846.

Sacks, J. J., Gonzales, K. R., Bouchery, E. E., Tomedi, L. E., & Brewer, R. D. (2015). 2010 national and state costs of excessive

alcohol consumption. American Journal of Preventive Medicine, 49, e73–e79.

Sacks, O. (1990). The man who mistook his wife for a hat and other clinical tales. New York, NY: HarperPerennial.

Sacks, O. (1995). An anthropologist on Mars. New York, NY: Vintage Books.

Sacks, O., & Wasserman, R. (1987, November 19). The case of the color-blind painter. New York Review of Books, 34, 25–34.

Saey, T. H. (2019, May 9). A gut bacteria transplant may not help you lose weight. ScienceNews. Retrieved from https://www.sciencenews.org/article/fecal-transplant-gut-bacteria-microbiome-weight

Safavi-Hemani, H., Gajewiak, J., Karanth, S., Robinson, S. D., Ueberheide, B., Douglass, A. D., et al. (2015). Specialized insulin is used for chemical warfare by fish-hunting cone snails. Proceedings of the National Academy of Sciences, 112, 1743–1748.

Saha, S., Chant, D., & McGrath, J. (2005). A systematic review of the prevalence of schizophrenia. PLoS Medicine, 2, 413–433.

Sahoo, S., Padhy, S. K., Padhee, B., Singla, N., & Sarkar, S. (2018). Role of personality in cardiovascular diseases: An issue that needs to be focused too! Indian Heart Journal, 70, S471–S477.

Saini, S. M., Mancuso, S. G., Mostaid, M. S., Liu, C., Pantelis, C., Everall, I. P. et al. (2017). Meta-analysis supports GWAS-implicated link between GRM3 and schizophrenia risk. Translational Psychiatry, 7, e1196.

Sairanen, M., Lucas, G., Ernfors, P., Castrén, M., & Castrén, E. (2005). Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. Journal of Neuroscience, 25, 1089–1094.

Sakata, H., Takaoka, Y., Kawarasaki, A., & Shibutani, H. (1973). Somatosensory properties of neurons in the superior parietal cortex (area 5) of the rhesus monkey. Brain Research, 64, 85–102.

Salamy, J. (1970). Instrumental responding to internal cues associated with REM sleep. Psychonomic Science, 18, 342–343.

Saleem, F., & Rizvi, S. W. (2017). Transgender associations and possible etiology: A literature review. Cureus, 9(12), e1984. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5825045

Salomons, T. V., Coan, J. A., Hunt, S. M., Backonja, M.-M., & Davidson, R. J. (2008). Voluntary facial displays of pain increase suffering in response to nociceptive stimulation. Journal of Pain, 9, 443–448.

Samara, M. T., Dold, M., Gianatsi, M., Nikolakopoulou, A., Helfer, B., Salanti, G., et al. (2016). Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: A network meta-analysis. JAMA Psychiatry, 73, 199–210.

Sanacora, G., Mason, G. F., Rothman, D. L., Hyder, F., Ciarcia, J. J., Osroff, R. B., et al. (2003). Increased cortical GABA concentrations in depressed patients receiving ECT. American Journal of Psychiatry, 160, 577–579.

Sanders, A. R., Martin, E. R., Beecham, G. W., Guo, S., Dawood, K., Rieger, G., et al. (2015). Genome-wide scan demonstrates

significant linkage for male sexual orientation. Psychological Medicine, 45, 1379–1388.

Sanders, A. R., Martin, E. R., Beecham, G. W., Guo, S., Dawood, K., Rieger, G., et al. (2017). Genome-wide association study of male sexual orientation. Scientific Reports, 7, 16950. Retrieved from https://www.nature.com/articles/s41598-017-15736-4

Sandhu, A., Seth, M., & Gurm, H. S. (2014). Daylight savings time and myocardial infarction. Open Heart, 1(1), e000019. doi:10.1136/openhrt-2013-000019.

Sandin, S., Lichtenstein, P., Kuja-Halkola, R., Hultman, C., Larsson, H., & Reichenberg, A. (2017). The heritability of autism spectrum disorder. Journal of the American Medical Association, 318, 1182–1184.

Sani, O. G., Yang, Y., Lee, M. B., Dawes, H. E., Chang, E. F., & Shanechi, M. M. (2013). Mood variations decoded from multi-site intracranial human brain activity. Nature Biotechnology, 36, 954–961.

Santana, G. L., Coelho, B. M., Borges, G., Viana, M. C., Wang, Y. P., & Andrade, L. H. (2015). The influence of parental psychopathology on offspring suicidal behavior across the lifespan. PLoS One, 10, e0134970.

Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., et al. (2003). Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science, 301, 805–809.

Santini, E., Muller, R. U., & Quirk, G. J. (2001). Consolidation of extinction learning involves transfer from NMDA-independent to NMDA-dependent memory. Journal of Neuroscience, 21, 9009–9017.

Sanz, C., Cali, J., & Morgan, D. (2009). Design complexity in termite-fishing tools of chimpanzees (*Pan troglodytes*). Biology Letters, 5, 293–296.

Sanz, L. R. D., LeJeune, N., Blandiaux, S., Bonin, E., Thibaut, A., Stender, J., et al. (2019). Treating disorders of consciousness with apomorphine: Protocol for a double-blind randomized controlled trial using multimodal assessments. Frontiers in Neurology, 10, 248. Retrieved from https://doi.org/10.3389/fneur.2019.00248

Saper, C. B., Chou, T. C., & Elmquist, J. K. (2002). The need to feed: Homeostatic and hedonic control of eating. Neuron, 36, 199–211.

Saper, C. B., Fuller, P. M., Pedersen, N. P., Lu, J., & Scammell, T. E. (2010). Sleep state switching. Neuron, 68, 1023–1042.

Sapolsky, R. M., Uno, H., Rebert, C. S., & Finch, C. E. (1990). Hippocampal damage associated with prolonged glucocorticoid exposure in primates. Journal of Neuroscience, 10, 2897–2902.

Şar, V., Dorahy, M., & Krüger, C. (2017). Revisiting the etiological aspects of dissociative identity disorder: A biopsychosocial perspective. Psychology Research and Behavioral Management, 10, 137–146.

Sarachana, T., & Hu, V. W. (2013). Genome-wide identification of transcriptional targets of RORA reveals direct regulation of multiple genes associated with autism spectrum disorder. Molecular Autism, 4, 14. Retrieved from http://www.molecularautism.com/content/4/1/14

Saraswat, A., Weinand, J. D., & Safer, J. D. (2015). Evidence supporting the biologic nature of gender identity. Endocrine Practice, 21, 199–204.

Sáry, G., Vogels, R., & Orban, G. A. (1993). Cue-invariant shape selectivity of macaque inferior temporal neurons. Science, 260, 995–997.

Sata, R., Maloku, E., Zhubi, A., Pibiri, F., Hajos, M., Costa, E., et al. (2008). Nicotine decreases DNA methyltransferase 1 expression and glutamic acid decarboxylase 67 promoter methylation in GABAergic interneurons. Proceedings of the National Academy of Sciences, 105, 16356–16361.

Savage-Rumbaugh, E. S., Murphy, J., Sevcik, R. A., Brakke, K. E., Williams, S. L., & Rumbaugh, D. M. (1993). Language comprehension in ape and child. Monographs of the Society for Research in Child Development, 58, 1–222.

Savage-Rumbaugh, S. (1987). A new look at ape language: Comprehension of vocal speech and syntax. *Nebraska Symposium on Motivation*, 35, 201–255.

Savage-Rumbaugh, S., McDonald, K., Sevcik, R. A., Hopkins, W. D., & Rubert, E. (1986). Spontaneous symbol acquisition and communicative use by pygmy chimpanzees (*Pan paniscus*). Journal of Experimental Psychology: General, 115, 211–235.

Savic, I., Berglund, H., & Lindström, P. (2005). Brain response to putative pheromones in homosexual men. Proceedings of the National Academy of Sciences, 102, 7356–7361.

Savic, I., & Lindström, P. (2008). PET and MRI show differences in cerebral asymmetry and functional connectivity between homo- and heterosexual subjects. Proceedings of the National Academy of Sciences, 105, 9403–9408.

Savica, R. (2014, June 18). Silenced by dementia: What happened to Casey Kasem. University of Utah HealthFeed. Retrieved from

http://healthcare.utah.edu/healthfeed/postings/2014/06/061814_kasem.silenced.php

Savin-Williams, R. C. (1996). Self-labeling and disclosure among gay, lesbian, and bisexual youths. In J. Laird & R.-J. Green (Eds.), Lesbians and gays in couples and families: A handbook for therapists (pp. 153–182). San Francisco, CA: Jossey-Bass.

Sawa, A., & Snyder, S. H. (2002). Schizophrenia: Diverse approaches to a complex disease. Science, 296, 692–695.

Sawchenko, P. E. (1998). Toward a new neurobiology of energy balance, appetite, and obesity: The anatomists weigh in. Journal of Comparative Neurology, 402, 435–441.

Scahill, L., Bitsko, R. H., Visser, S. N., & Blumberg, S. J. (2009). Prevalence of diagnosed Tourette syndrome in persons aged 6–17 years—United States, 2007. Morbidity and Mortality Weekly Report. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5821a1.htm

Scarr, S., & Carter-Saltzman, L. (1982). Genetics and intelligence. In R. J. Sternberg (Ed.), Handbook of human intelligence (pp. 792–896). New York, NY: Cambridge University Press.

Scarr, S., Pakstis, A. J., Katz, S. H., & Barker, W. B. (1977). Absence of a relationship between degree of white ancestry and intellectual skills within a black population. Human Genetics, 39, 69–86.

Scarr, S., & Weinberg, R. A. (1976). IQ test performance of black children adopted by white families. American Psychologist, 31, 726–739.

Schachter, S., & Singer, J. E. (1962). Cognitive, social, and physiological determinants of emotional state. Psychological

Review, 69, 379–399.

Schacter, D. L., Alpert, N. M., Savage, C. R., Rauch, S. L., & Albert, M. S. (1996). Conscious recollection and the human hippocampal formation: Evidence from positron emission tomography. Proceedings of the National Academy of Sciences, 93, 321–325.

Schacter, D. L., & Wagner, A. D. (1999). Remembrance of things past. Science, 285, 1503–1504.

Schaie, K. W. (1994). The course of adult intellectual development. American Psychologist, 49, 304–311.

Schapiro, A. C., McDevitt, E. A., Rogers, T. T., Mednick, S. C., & Norman, K. A. (2018). Human hippocampal replay during rest prioritizes weakly learned information and predicts memory performance. Nature Communications, 9, 3920. Retrieved from https://www.nature.com/articles/s41467-018-06213-1

Scheele, D., Wille, A., Kendrick, K. M., Stoffel-Wagner, B., Becker, B., Güntürkün, O., et al. (2013). Oxytocin enhances brain reward system responses in men viewing the face of their female partner. Proceedings of the National Academy of Sciences, 110(50), 20308–20313. https://doi.org/10.1073/pnas.1314190110

Schein, S. J., & Desimone, R. (1990). Spectral properties of V4 neurons in the macaque. Journal of Neuroscience, 10, 3369–3389.

Schelter, B. O., Shiells, H., Baddeley, T. C., Rubino, C. M., Ganesan, H., Hammel, J., et al. (2019). Concentration-dependent activity of hydromethylthionine on cognitive decline and brain atrophy in mild to moderate Alzheimer’s disease. Journal of Alzheimer’s Disease, 72, 931–946.

Schenck, C. H., Milner, D. M., Hurwitz, T. D., Bundlie, S. R., & Mahowald, M. W. (1989). A polysomnographic and clinical report on sleep-related injury in 100 adult patients. American Journal of Psychiatry, 146, 1166–1173.

Scherag, S., Hebebrand, J., & Hinney, A. (2009). Eating disorders: The current status of molecular genetic research. European Child and Adolescent Psychiatry. doi:10.1007/s00787-009-0085-9

Scherf, S., Behrmann, M., Minshew, N., & Luna, B. (2008). Atypical development of face and greeble recognition in autism. Journal of Child Psychiatry, 49, 838–847.

Schiff, N. D., Giacino, J. T., Kalmar, K., Victor, J. D., Baker, K., Gerber, M., et al. (2007). Behavioral improvements with thalamic stimulation after severe traumatic brain injury. Nature, 448, 600–604.

Schildkraut, J. J. (1965). The catecholamine hypothesis of affective disorders: A review of supporting evidence. American Journal of Psychiatry, 122, 509–522.

Schiller, D., Monfils, M.-H., Raio, C. M., Johnson, D. C., LeDoux, J. E., & Phelps, E. A. (2010). Preventing the return of fear in humans using reconsolidation update mechanisms. Nature, 463, 49–53.

Schiller, P. H., & Logothetis, N. K. (1990). The color-opponent and broadband channels of the primate visual system. Trends in Neurosciences, 13, 392–398.

Schindler, S., Schmidt, L., Stroske, M., Storch, M., Anwander, A., Trampel, R., et al. (2019). Hypothalamus enlargement in mood disorders. Acta Psychiatrica Scandinavica, 139, 56–67.

Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2014). Biological insights from 108 schizophrenia-associated genetic loci. Nature, 511, 421–427.

Schmidt, S. L., Harmon, K. A., Sharp, T. A., Kealey, E. H., & Bessesen, D. H. (2012). The effects of overfeeding on spontaneous physical activity in obesity prone and obesity resistant humans. Obesity, 20, 2186–2193.

Schmidt, S. L., Kealey, E. H., Horton, T. J., VonKaenel, S., & Bessesen, D. H. (2013). The effects of short-term overfeeding on energy expenditure and nutrient oxidation in obesity-prone and obesity-resistant individuals. International Journal of Obesity, 37, 1192–1197.

Schnakers, C., Vanhaudenhuyse, A., Giacino, J., Ventura, M., Boly, M., Majerus, S., et al. (2009). Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. BMC Neurology, 9, 35. Retrieved from http://www.biomedcentral.com/1471–2377/9/35

Schneiderman, I., Zagoory-Sharon, O., Leckman, J. F., & Feldman, R. (2012). Oxytocin during the initial stages of romantic attachment: relations to couples' interactive reciprocity. Psychoneuroendocrinology, 37, 1277–1285.

Schnider, A. (2003). Spontaneous confabulation and the adaptation of thought to ongoing reality. Nature Reviews Neuroscience, 4, 662–671.

Schobel, S. A., Lewandowski, N. M., Corcoran, C. M., Moore, H., Brown, T., Malaspina, D., et al. (2009). Differential targeting of the CA1 subfield of the hippocampal formation by schizophrenia and related psychotic disorders. Archives of General Psychiatry, 66, 938–946.

Schober, M. E., Requena, D. F., Abdullah, O. M., Casper, T. C., Beach, J., Malleske, D., & Pauly, J. R. (2016). Dietary docosahexaenoic acid improves cognitive function, tissue sparing, and magnetic resonance imaging indices of edema and white matter injury in the immature rat after traumatic brain injury. Journal of Neurotrauma, 33(4), 390–402. doi:10.1089/neu.2015.3945

Schoenfeld, M. A., Neuer, G., Tempelmann, C., Schübler, K., Noesselt, T., Hopf, J.-M., et al. (2004). Functional magnetic resonance tomography correlates of taste perception in the human primary taste cortex. Neuroscience, 127, 347–353.

Schreiber, R., Melon, C., & DeVry, J. (1998). The role of 5-HT receptor subtypes in the anxiolytic effects of selective serotonin reuptake inhibitors in the rat ultrasonic vocalization test. Psychopharmacology, 135, 383–391.

Schreiweis, C., Bornschein, U., Burguiere, E., Kerimoglu, C., Schreiter, S., Dannemann, M., et al. (2014). Humanized Foxp2 accelerates learning by enhancing transitions from declarative to procedural performance. Proceedings of the National Academy of Sciences, 111(39), 14253–14258.

Schubert, A.-L., Hagermann, D., & Frischkom, G. T. (2017). Is general intelligence little more than the speed of higher-order processing? Journal of Experimental Psychology: General, 146, 1498–1512.

Schuckit, M. A. (1994). Low level of response to alcohol as a predictor of future alcoholism. American Journal of Psychiatry, 151, 184–189.

Schull, W. J., Norton, S., & Jensh, R. P. (1990). Ionizing radiation and the developing brain. Neurotoxicology and Teratology, 12, 249–260.

Schulsinger, F., Parnas, J., Petersen, E. T., Schulsinger, H., Teasdale, T. W., Mednick, S. A., et al. (1984). Cerebral ventricular size in the offspring of schizophrenic mothers. Archives of General Psychiatry, 41, 602–606.

Schultz, W. (2016). Dopamine reward prediction error coding. Dialogues in Clinical Neuroscience, 18, 23–32.

Schwartz, B. L., & Krantz, J. L. (2015). Sensation and perception. Thousand Oaks, CA: SAGE.

Schwartz, J. M., Stoessel, P. W., Baxter, L. R., Martin, K. M., & Phelps, M. E. (1996). Systematic changes in cerebral glucose metabolic rate after successful behavior modification treatment of obsessive-compulsive disorder. Archives of General Psychiatry, 53, 109–113.

Schwartz, M. S. (1994). Ictal language shift in a polyglot. Journal of Neurology, Neurosurgery, and Psychiatry, 57, 121.

Schwartz, M. W., & Seeley, R. J. (1997). The new biology of body weight regulation. Journal of the American Dietetic Association, 97, 54–58.

Schwartz, R. (2015, June 9). Breakthrough lets amputees “feel” their artificial limbs. The Daily Good. Retrieved from https://www.good.is/articles/prosthetic-limb-lets-amputees-feel-ends-phantom-limb-pain

Schwartz, W. J., & Gainer, H. D. (1977). Suprachiasmatic nucleus: Use of 14C-labeled deoxyglucose uptake as a functional marker. Science, 197, 1089–1091.

Science News Staff. (2019, March 25). Duke University settles research misconduct lawsuit for $112.5 million. Science. Retrieved

from https://www.sciencemag.org/news/2019/03/duke-university-settles-research-misconduct-lawsuit-1125-million

Scott, E. M., & Verney, E. L. (1947). Self-selection of diet: VI. The nature of appetites for B vitamins. Journal of Nutrition, 34, 471–480.

Scott, T. R. (2011). Learning through the taste system. Frontiers in Systems Neuoscience, 5, Article 8. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3222881

Sedaris, D. (1998). Naked. Boston, MA: Little, Brown.

Sedlak, T. W., Nucifora, L. G., Koga, M., Shaffer, L. S., Higgs, C., Tanaka, T., et al. (2017). Sulforaphane augments glutathione and influences brain metabolites in human subjects: A clinical pilot study. Molecular Neuropsychiatry, 3, 214–222.

Seeman, P., Lee, T., Chau-Wong, M., & Wong, K. (1976). Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature, 261, 717–719.

Seiger, R., Hahn, A., Hummer, A., Kranz, G. S., Ganger, S., Woletz, M., et al. (2016). Subcortical gray matter changes in transgender subjects after long-term cross-sex hormone administration. Psychoneuroendocrinology, 74, 371–379.

Sejnowski, T. J., & Rosenberg, C. R. (1987). Parallel networks that learn to pronounce English text. Complex Systems, 1, 145–168.

Sekiguchi, A., Kotozaki, Y., Sugiura, M., Nouchi, R., Takeuchi, H., Hanawa, S., et al. (2014). Resilience after 3/11: Structural brain changes 1 year after the Japanese earthquake. Molecular Psychiatry, 20, 553–554.

Sekiguchi, A., Sugiura, M., Taki, Y., Kotozaki, Y., Nouchi, R., Takeuchi, H., et al. (2013). Brain structural changes as vulnerability factors and acquired signs of post-earthquake stress. Molecular Psychiatry, 18, 618–623.

Selfe, L. (1977). Nadia: A case of extraordinary drawing ability in children. London, UK: Academic Press.

Selkoe, D. J. (1997). Alzheimer's disease: Genotypes, phenotype, and treatments. Science, 275, 630–631.

Sellers, E. W., Ryan, D. B., & Hauser, C. K. (2014). Noninvasive brain-computer interface enables communication after brainstem stroke. Science Translational Medicine, 6(257), 257re7. doi:10.1126/scitranslmed.3007801

Semenya out of World Championships after Swiss court reverses reprieve. (2019, July 30). Reuters. Retrieved from https://www.reuters.com/article/us-athletics-semenya/semenya-out-of-world-championships-after-swiss-court-reverses-reprieve-idUSKCN1UP27A

Sendt, K.-V., Giaroli, G., & Tracy, D. K. (2012). Beyond dopamine: Glutamate as a target for future antipsychotics. ISRN Pharmacology, 2012, 427267. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3399404

Senghas, A., Kita, S., & Özyürek, A. (2004). Children creating core properties of language: Evidence from an emerging sign language in Nicaragua. Science, 305, 1779–1782.

Senju, A., Maeda, M., Kikuchi, Y., Hasegawa, T., Tojo, Y., & Osanai, H. (2007). Absence of contagious yawning in children with autism spectrum disorder. Biology Letters. doi:10.1098/rsb1.2007.0337

Sepkowitz, K. A. (2013). Energy drinks and caffeine-related adverse events. Journal of the American Medical Association, 309, 243–244.

Sergent, C., Baillet, S., & Dehaene, S. (2005). Timing of the brain events underlying access to consciousness during the attentional blink. Nature Neuroscience, 8, 1391–1400.

Servick, K. (2018, November). Mysterious new brain cell found in people. Science Magazine. Retrieved from https://www.sciencemag.org/news/2018/08/mysterious-new-brain-cell-found-people

Sevigny, J., Chiao, P., Bussière, T., Weinreb, P. H., Williams, L, Maier, M., et al. (2016). The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature, 537, 50–56.

Shadrina, M., Bondarenko, E. A., & Slominsky, P. A. (2018). Genetics factors in major depression disease. Frontiers in Psychiatry. Retrieved from https://doi.org/10.3389/fpsyt.2018.00334

Shaffery, J. P., Roffwarg, H. P., Speciale, S. G., & Marks, G. A. (1999). Ponto-geniculo-occipital-wave suppression amplifies lateral geniculate nucleus cell-size changes in monocularly deprived kittens. Brain Research. Developmental Brain Research, 114, 109–119.

Shah, A., & Lisak, R. P. (1993). Immunopharmacologic therapy in myasthenia gravis. Clinical Neuropharmacology, 16, 97–103.

Shalev, A. Y., Peri, T., Brandes, D., Freedman, S., Orr, S. P., & Pittman, R. K. (2000). Auditory startle response in trauma survivors with posttraumatic stress disorder: A prospective study. American Journal of Psychiatry, 157, 255–261.

Sham, P. C., O'Callaghan, E., Takei, N., Murray, G. K., Hare, E. H., & Murray, R. M. (1992). Schizophrenia following pre-natal exposure to influenza epidemics between 1939 and 1960. British Journal of Psychiatry, 160, 461–466.

Shankland, S. (2018, September 12). iPhone XS A12 Bionic chip is industry-first 7nm CPU. CNET. Retrieved from https://www.cnet.com/news/iphone-xs-a12-bionic-chip-is-industry-first-7nm-cpu

Shapiro, C. M., Bortz, R., Mitchell, D., Bartel, P., & Jooste, P. (1981). Slow-wave sleep: A recovery period after exercise. Science, 214, 1253–1254.

Shapiro, M. L., Tanila, H., & Eichenbaum, H. (1997). Cues that hippocampal place cells encode: Dynamic and hierarchical representation of local and distal stimuli. Hippocampus, 7, 624–642.

Shepard, R. N. (1990). Mind sights: Original visual illusions, ambiguities, and other anomalies, with a commentary on the play of mind in perception in art. New York, NY: W. H. Freeman & Co.

Sherman, G. D., Lerner, J. S., Josephs, R. A., Renshon, J., & Gross, J. J. (2015). The interaction of testosterone and cortisol is associated with attained status in male executives. Journal of Personality and Social Psychology, 110, 921–929.

Sherva, R., Wilhelmsen, K., Pomerleau, C. S., Chasse, S. A., Rice, J. P., Snedecor, S. M., et al. (2008). Association of a single nucleotide polymorphism in neuronal acetylcholine receptor subunit alpha 5 (CHRNA5) with smoking status and with "pleasurable buzz" during early experimentation with smoking. Addiction, 103, 1544–1552.

Sherwin, B. B., & Gelfand, M. M. (1987). The role of androgen in the maintenance of sexual functioning in oophorectomized women. Psychosomatic Medicine, 49, 397–409.

Sheth, S. A., Neal, J., Tangherlini, F., Mian, M. K., Gentil, A., Cosgrove, G. R., et al. (2013). Limbic system surgery for treatment-refractory obsessive-compulsive disorder: A prospective long-term follow-up of 64 patients. Journal of Neurosurgery, 118, 491–497.

Shi, G., Xing, L., Wu, D., Bhattacharyya, B. J., Jones, C. R., McMahon, T., et al. (2019). A rare mutation of β1-adrenergic receptor affects sleep/wake behaviors. Neuron, 103, P1044–P1055.

Shi, Z., Araujo, A. B., Martin, S., O'Loughlin, P., & Wittert, G. A. (2013). Longitudinal changes in testosterone over five years in community-dwelling men. Journal of Clinical Endocrinology & Metabolism, 98, 3289–3297.

Shibata, D. K. (2007). Differences in brain structure in deaf persons on MR imaging studied with voxel-based morphometry. American Journal of Neuroradiology, 28, 243–249.

Shifren, J. L., Braunstein, G. D., Simon, J. A., Casson, P. R., Buster, J. E., Redmond, G. P., et al. (2000). Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. New England Journal of Medicine, 343, 682–688.

Shima, K., & Tanji, J. (2000). Neuronal activity in the supplementary and presupplementary motor areas for temporal organization of multiple movements. Journal of Neurophysiology, 84, 2148–2160.

Shimura, T., & Shimokochi, M. (1990). Involvement of the lateral mesencephalic tegmentum in copulatory behavior of male rats:

Neuron activity in freely moving animals. Neuroscience Research, 9, 173–183.

Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology Reviews, 35, 169–191.

Shirneshan, E. (2013). Cost of illness study of anxiety disorders for the ambulatory adult population of the United States. University of Tennessee Health Science Center. Unpublished doctoral dissertation. Retrieved from https://dc.uthsc.edu/dissertations/370

Shouse, M. N., & Siegel, J. M. (1992). Pontine regulation of REM sleep components in cats: Integrity of the pedunculopontine tegmentum (PPT) is important for phasic events but unnnecessary for atonia during REM sleep. Brain Research, 571, 50–63.

Shuai, Y., Lu, B., Hu, Y., Wang, L., Sun, K., & Zhong, Y. (2010). Forgetting is regulated through Rac activity in *Drosophila*. Cell, 140, 579–589.

Shulgin, A., & Shulgin, A. (1991). Pihkal: A chemical love story. Lafayette, CA: Transform Press.

Shulgin, A., & Shulgin, A. (1997). TIHKAL: The continuation. Berkeley, CA: Transform Press.

Shulman, L. M., & Spritzer, M. D. (2014). Changes in the sexual behavior and testosterone levels of male rats in response to daily interactions with estrus females. Physiology and Behavior, 133, 8–13.

Siclari, F., Baird, B., Perogamvros, L., Bernardi, G., LaRocque, J., Riedner, B., et al. (2017). The neural correlates of dreaming. Nature Neuroscience, 20, 872–878.

Siegel, S. (1984). Pavlovian conditioning and heroin overdose: Reports by overdose victims. Bulletin of the Psychonomic Society, 22, 428–430.

Siegel, S., Hinson, R. E., Krank, M. D., & McCully, J. (1982). Heroin "overdose" death: Contribution of drug-associated environmental cues. Science, 216, 436–437.

Siegelbaum, S. A., & Kandel, E. R. (2013). Overview of synaptic transmission. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), Principles of neural science (5th ed., pp. 177–188). New York, NY: McGraw-Hill.

Siegelbaum, S. A., Kandel, E. R., & Yuste, R. (2013). Synaptic integration in the central nervous system. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), Principles of neural science (5th ed., pp. 210–235). New York, NY: McGraw-Hill.

Siepel, A., Bejerano, G., Pedersen, J. S., Hinrichs, A. S., Hou, M., Rosenbloom, K., et al. (2005). Evolutionarily conserved elements in vertebrate, insect, worm, and yeast genomes. Genome Research, 15, 1034–1050.

Siever, L. J., Kahn, R. S., Lawlor, B. A., Trestman, R. L., Lawrence, T. L., & Coccaro, E. F. (1991). II. Critical issues in defining the role of serotonin in psychiatric disorders. Pharmacological Reviews, 43, 509–525.

Silbersweig, D. A., Stern, E., Frith, C., Cahill, C., Homes, A., Grootoonk, S., et al. (1995). A functional neuroanatomy of hallucinations in schizophrenia. Nature, 378, 176–179.

Silinsky, E. M. (1989). Adenosine derivatives and neuronal function. Seminars in the Neurosciences, 1, 155–165.

Simner, J., Mulvenna, C., Sagiv, N., Tsakanikos, E., Witherby, S. A., Fraser, C., et al. (2006). Synesthesia: The prevalence of atypical cross-modal experiences. Perception, 35, 1024–1033.

Simos, P. G., Castillo, E. M., Fletcher, J. M., Francis, D. J., Maestu, F., Breier, J. I., et al. (2001). Mapping of receptive language cortex in bilingual volunteers by using magnetic source imaging. Journal of Neurosurgery, 95, 76–81.

Simpson, J. L., Ljungqvist, A., de la Chapelle, A., Ferguson-Smith, M. A., Genel, M., Carlson, A. S., et al. (1993). Gender verification in competitive sports. Sports Medicine, 16, 305–315.

Sinclair, H. (2017, September 26). Trump says he is scared of germs and needs to drink from a straw to avoid contamination. Newsweek. Retrieved from https://www.newsweek.com/trump-scared-germs-needs-drink-straw-avoid-contamination-671730

Singer, T., O'Doherty, S. B., Kaube, H., Dolan, R. J., & Frith, C. D. (2004). Empathy for pain involves the affective but not sensory components of pain. Science, 303, 1157–1162.

Singer, W. (1995). Development and plasticity of cortical processing architectures. Science, 270, 758–764.

Siniscalco, D., Cirillo, A., Bradstreet, J. J., & Antonucci, N. (2013). Epigenetic findings in autism: New perspectives for therapy. International Journal of Environmental Research and Public Health, 10, 4261–4273.

Sivian, L. J., & White, S. D. (1933). On minimum audible fields. Journal of the Acoustical Society of America, 4, 288–321.

Sjöström, L., Narbro, K., Sjöström, D., Karason, K., Larsson, B., Wedel, H., et al. (2007). Effects of bariatric surgery on mortality in

Swedish obese subjects. New England Journal of Medicine, 357, 741–752.

Slimp, J. C., Hart, B. L., & Goy, R. W. (1978). Heterosexual, autosexual and social behavior of adult male rhesus monkeys with medial preopticanterior hypothalamic lesions. Brain Research, 142, 105–122.

Small, S. A., Stern, Y., Tang, M., & Mayeux, R. (1999). Selective decline in memory function among healthy elderly. Neurology, 52, 1392–1396.

Small, furry … and smart. (2009). Nature, 461, 862–864.

Smalley, S. L. (1997). Genetic influences in childhood-onset psychiatric disorders: Autism and attention-deficit/hyperactivity disorder. American Journal of Human Genetics, 60, 1276–1282.

Smith, C. (1995). Sleep states and memory processes. Behavioural Brain Research, 69, 137–145.

Smith, C. N., & Squire, L. R. (2009). Medial temporal lobe activity during retrieval of semantic memory is related to the age of the memory. Journal of Neuroscience, 29, 930–938.

Smith, D. H. (2009). Stretch growth of integrated axon tracts: Extremes and exploitations. Progress in Neurobiology, 89, 231–239.

Smith, D. M., & Atkinson, R. M. (1995). Alcoholism and dementia. International Journal of Addiction, 30, 1843–1869.

Smith, D. M., & Mizumori, S. J. Y. (2006). Hippocampal place cells, context, and episodic memory. Hippocampus, 16, 716–729.

Smith, E. S., Junger, J., Derntl, B., & Habel, U. (2015). The transsexual brain—A review of findings on the neural basis of transsexualism. Neuroscience and Biobehavioral Reviews, 59, 251–266.

Smith, J., Cianflone, K., Biron, S., Hould, F. S., Lebel, S., Marceau, S., et al. (2009). Effects of maternal surgical weight loss in mothers on intergenerational transmission of obesity. Journal of Clinical Endocrinology and Metabolism, 94, 4275–4283.

Smith, M. A., Brandt, J., & Shadmehr, R. (2000). Motor disorder in Huntington's disease begins as a dysfunction in error feedback control. Nature, 403, 544–549.

Smith, M. J., Keel, J. C., Greenberg, B. D., Adams, L. F., Schmidt, P. J., Rubinow, D. A., et al. (1999). Menstrual cycle effects on cortical excitability. Neurology, 53, 2069–2072.

Smith, P. H., Homish, G. G., Giovino, G. A., & Kozlowski, L. T. (2014). Cigarette smoking and mental illness: A study of nicotine withdrawal. American Journal of Public Health, 104(2), e127–133. doi:10.2105/AJPH.2013.301502

Smith, T. (2013, December 12). Newtown parents seek a clear window into violent behavior. NPR Morning Edition. Retrieved from http://www.npr.org/2013/12/12/250287971/newtown-parents-seek-a-clearer-window-into-violent-behavior

Smucny, J., Stevens, K. E., Olincy, A., & Tregellas, J. R. (2015). Translational utility of rodent hippocampal auditory gating in schizophrenia research: A review and evaluation. Translational Psychiatry, 5, e587.

Snowball, A., Tachtsidis, I., Popescu, T., Thompson, J., Delazer, M., Zamarian, L., et al. (2013). Long-term enhancement of brain

function and cognition using cognitive training and brain stimulation. Current Biology, 23, 987–992.

Snyder, A. (2009). Explaining and inducing savant skills: Privileged access to lower level, less-processed information. Philosophical Transactions of the Royal Society B, 364, 1399–1405.

Snyder, A. W., & Mitchell, D. J. (1999). Is integer arithmetic fundamental to mental processing? The mind's secret arithmetic. Proceedings of the Royal Society of London B, 266, 587–592.

Snyder, S. H. (1972). Catecholamines in the brain as mediators of amphetamine psychosis. Archives of General Psychiatry, 27, 169–179.

Snyder, S. H. (1984). Drug and neurotransmitter receptors in the brain. Science, 224, 22–31.

Snyder, S. H. (1997). Knockouts anxious for new therapy. Nature, 388, 624.

Society for Neuroscience. (n.d.). Policies on the use of animals and humans in research. Retrieved from https://www.sfn.org/Advocacy/Policy-Positions/Policies-on-the-Use-of-Animals-and-Humans-in-Research

Söderlund, J., Schröder, J., Nordin, C., Samuelsson, M., Walther-Jallow, L., Karlsson, H., et al. (2009). Activation of brain interleukin-1b in schizophrenia. Molecular Psychiatry, 14, 1069–1071.

Sörensen, H. J., Nielsen, P. R., Pedersen, C. B., Benros, M. E., Nordentoft, M., & Mortensen, P. B. (2014). Population impact of familial and environmental risk factors for schizophrenia: A nationwide study. Schizophrenia Research, 153, 214–219.

Soria, V., Martinez-Amorós, È., Crespo, J. M., Martorell, L., Vilella, E., Labad, A., et al. (2010). Differential association of circadian genes with mood disorders: CRY1 and NPAS2 are associated with unipolar major depression and CLOCK and VIP with bipolar disorder. Neuropsychopharmacology, 35, 1279–1289.

Sotiriadis, A., & Makrydimas, G. (2012). Neurodevelopment after prenatal diagnosis of isolated agenesis of the corpus callosum: An integrative review. American Journal of Obstetrics & Gynecology, 206, 337e1–337e5. Retrieved from http://www.ajog.org/article/S0002-9378(11)02432-X

Soto-Otero, R., Méndez-Alvarez, E., Sánchez-Sellero, J., Cruz-Landeira, A., & López-Rivadulla, L. M. (2001). Reduction of rat brain levels of the endogenous dopaminergic proneurotoxins 1,2,3,4-tetrahydroisoquinoline and 1,2,3,4-tetrahydro-beta-carboline by cigarette smoke. Neuroscience Letters, 298, 187–190.

Sowell, E. R., Thompson, P. M., Holmes, C. J., Jernigan, T. L., & Toga, A. W. (1999). *In vivo* evidence for post-adolescent brain maturation in frontal and striatal regions. Nature Neuroscience, 2, 859–861.

Spalding, K. L., Bergmann, O., Alkass, K., Bernard, S., Salehpour, M., Huttner, H. B., et al. (2013). Dynamics of hippocampal neurogenesis in adult humans. Cell, 153, 1219–1227.

Sparing, R., & Mottaghy, F. M. (2008). Noninvasive brain stimulation with transcranial magnetic or direct current stimulation (TMS/tDCS)—From insights into human memory to therapy of its dysfunction. Methods, 44, 329–337.

Spearman, C. (1904). The proof and measurement of association between two things. American Journal of Psychology, 15, 72–101.

Spence, S. A., Brooks, D. J., Hirsch, S. R., Liddle, P. F., Mechan, J., & Grasby, P. (1997). A PET study of voluntary movement in schizophrenic patients experiencing passivity phenomena (delusions of alien control). Brain, 120, 1997–2011.

Spencer, K. M., Nestor, P. G., Permutter, R., Nizmikiewicz, M. A., Klump, M. C., Frumin, M., et al. (2004). Neural synchrony indexes disordered perception and cognition in schizophrenia. Proceedings of the National Academy of Sciences, 101, 17288–17293.

Spencer, K. M., Niznikiewicz, M. A., Nestor, P. G., Shenton, M. E., & McCarley, R. W. (2009). Left auditory cortex gamma synchronization and auditory hallucination symptoms in schizophrenia. BMC Neuroscience. Retrieved from http://www.biomedcentral.com/1471–2202/10/85

Sperling, R. A., Donohue, M. C., Raman, R., Sun, C.-K., Yaari, R., Holdridge, K., et al. (2020). Association of factors with elevated amyloid burden in clinically normal older individuals. JAMA Neurology, 77(6), 735–745. Retrieved from https://jamanetwork.com/journals/jamaneurology/article-abstract/2763540

Sperry, R. W. (1943). Effect of 180 degrees rotation of the retinal field on visuomotor coordination. Journal of Experimental Zoology, 92, 263–279.

Sperry, R. W. (1945). Restoration of vision after crossing of optic nerves and after contralateral transplantation of eye. Journal of Neurophysiology, 8, 15–28.

Spetter, M. S., de Graaf, C., Mars, M., Viergever, M. A., & Smeets, P. A. M. (2014). The sum of its parts—Effects of gastric distention, nutrient content and sensory stimulation on brain activation. PLoS ONE, 9(3), e90872.

Spiegel, D. (1996). Cancer and depression. British Journal of Psychiatry, 168, 109–116.

Spillantini, M. G., Schmidt, M. L., Lee, V. M.-Y., Trojanowski, J. Q., Jakes, R., & Goedert, M. (1997). a-Synuclein in Lewy bodies. Nature, 388, 839–840.

Spinney, L. (2002, September 21). The mind readers. New Scientist, 38–41.

Spreux-Varoquaux, O., Alvarez, J.-C., Berlin, I., Batista, G., Despierre, P.-G., Gilton, A., et al. (2001). Differential abnormalities in plasma 5-HIAA and platelet serotonin concentrations in violent suicide attempters: Relationships with impulsivity and depression. Life Sciences, 69, 647–657.

Spurzheim, J. G. (1908). Phrenology (Rev. ed.). Philadelphia, PA: Lippincott.

Squire, L. R. (2009). The legacy of Patient H.M. for neuroscience. Neuron, 61, 6–9.

Squire, L. R., & Alvarez, P. (1995). Retrograde amnesia and memory consolidation: A neurobiological perspective. Current Opinion in Neurobiology, 5, 169–177.

Squire, L. R., Amaral, D. G., & Press, G. A. (1990). Magnetic resonance imaging of the hippocampal formation and mammillary nuclei distinguish medial temporal lobe and diencephalic amnesia. Journal of Neuroscience, 10, 3106–3117.

Squire, L. R., Amaral, D. G., Zola-Morgan, S., Kritchevsky, M., & Press, G. (1989). Description of brain injury in the amnesic patient N.A. based on magnetic resonance imaging. Experimental Neurology, 105, 23–35.

Squire, L. R., Ojemann, J. G., Miezin, F. M., Petersen, S. E., Videen, T. O., & Raichle, M. E. (1992). Activation of the hippocampus in normal humans: A functional anatomical study of memory. Proceedings of the National Academy of Sciences, 89, 1837–1841.

Srinivasan, S., Bettella, F., Mattingsdal, M., Wang, Y., Witoelar, A., Schork, A. J., et al. (2016). Genetic markers of human evolution are enriched in schizophrenia. Biological Psychiatry, 80, 284–292.

Stahre, M., Roeber, J., Kanny, D., Brewer, R. D., & Zhang, X. (2014). Contribution of excessive alcohol consumption to deaths and years of potential life lost in the United States. Preventing Chronic Disease, 11, 130293.

Stanley, B. G., Kyrkouli, S. E., Lampert, S., & Leibowitz, S. F. (1986). Neuropeptide Y chronically injected into the hypothalamus: A powerful neurochemical inducer of hyperphagia and obesity. Peptides, 7, 1189–1192.

Starr, C., & Taggart, R. (1989). Biology: The unity and diversity of life. Pacific Grove, CA: Brooks/Cole.

St. Clair, D., Xu, M., Wang, P., Yu, Y., Fang, Y., Zhang, F., et al. (2005). Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959–1961. Journal of the American Medical Association, 294, 557–562.

Stein, J. (2001). The magnocellular theory of developmental dyslexia. Dyslexia, 7, 12–36.

Stein, J. L., Medland, S. E., Vasquez, A. A., Hibar, D. P., Senstad, R. E., Winkler, A. M., et al. (2012). Identification of common variants associated with human hippocampal and intracranial volumes. Nature Genetics, 44, 552–561.

Stein, M. B., McCarthy, M. J., Chen, C.-Y., Jain, S., Gelernter, J., He, F., et al. (2018). Genome-wide analysis of insomnia disorder. Molecular Psychiatry, 23, 2238–2250.

Stein, P. K., Soare, A., Meyer, T. E., Cangemi, R., Holloszy, J. O., & Fontana, L. (2012). Caloric restriction may reverse age-related autonomic decline in humans. Aging Cell, 11, 644–650.

Steinberg, E. E., Christoffel, D. J., Deisseroth, K., & Malenka, R. C. (2015). Illuminating circuitry relevant to psychiatric disorders with optogenetics. Current Opinion in Neurobiology, 30, 9–16.

Stellar, J. R., & Stellar, E. (1985). The neurobiology of motivation and reward. New York, NY: Springer-Verlag.

Stephan, F. K., & Nunez, A. A. (1977). Elimination of circadian rhythms in drinking, activity, sleep, and temperature by isolation of the suprachiasmatic nuclei. Behavioral Biology, 20, 1–16.

Stephens, D. N., & Duka, T. (2008). Cognitive and emotional consequences of binge drinking: Role of amygdala and prefrontal cortex. Philosophical Transactions of the Royal Society B, 363, 3169–3179.

Stephen Wiltshire MBE—Biography. (n.d.). Retrieved from http://www.stephenwiltshire.co.uk/biography.aspx

Steriade, M., Paré, D., Bouhassira, D., Deschênes, M., & Oakson, G. (1989). Phasic activation of lateral geniculate and perigeniculate thalamic neurons during sleep with ponto-geniculo-occipital waves. Journal of Neuroscience, 9, 2215–2229.

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurology, 11, 1006–1012.

Sternbach, R. A. (1968). Pain: A psychophysiological analysis. New York, NY: Academic Press.

Sternberg, R. J. (1988). The triarchic mind: A new theory of human intelligence. New York, NY: Viking.

Sternberg, R. J. (2000). The holey grail of general intelligence. Science, 289, 399–401.

Sternson, S. M., & Eiselt, A.-K. (2017). Three pillars for the neural control of appetite. Annual Review of Physiology, 79, 401–423.

Stickgold, R., Hobson, J. A., Fosse, R., & Fosse, M. (2001). Sleep, learning, and dreams: Off-line memory reprocessing. Science, 294, 1052–1057.

Stickgold, R., Whidbee, D., Schirmer, B., Patel, V., & Hobson, J. A. (2000). Visual discrimination task improvement: A multi-step process occurring during sleep. Journal of Cognitive Neuroscience, 12, 246–254.

Stopper, C. M., Khayambashi, S., & Floresco, S. B. (2013). Receptor-specific modulation of risk-based decision making by nucleus accumbens dopamine. Neuropsychopharmacology, 38, 715–728.

Strack, F., Martin, L. L., & Stepper, S. (1988). Inhibiting and facilitating conditions of the human smile: A nonobtrusive test of the facial feedback hypothesis. Journal of Personality and Social Psychology, 54, 768–777.

Strandqvist, A., Herlitz, A., Nordenskjöld, A., Örtqvist, l., Frisén, L., Hirschberg, A. L., & Nordenström, A. (2018). Cognitive abilities in women with complete androgen insensitivity syndrome and

women with gonadal dysgenesis. Psychoneuroendocrinology, 98, 233–241.

Strang, J., Babor, T., Caulkins, J., Fischer, B., Foxcroft, D., & Hunphreys, K. (2012). Drug policy and the public good: Evidence for effective interventions. Lancet, 379, 71–83.

Stratigopoulos, G., Carli, J. F. M., O'Day, D. R., Wang, L., LeDuc, C. A., Lanzano, P., et al. (2014). Hypomorphism for *RPGRIP1L*, a ciliary gene vicinal to the *FTO* locus causes increased adiposity in mice. Cell Metabolism, 19, 767–779.

Streissguth, A. P., Barr, H. M., Bookstein, F. L., Sampson, P. D., & Olson, H. C. (1999). The long-term neurocognitive consequences of prenatal alcohol exposure: A 14-year study. Psychological Science, 10, 186–190.

Studer, B., Manes, F., Humphreys, G., Robbins, T. W., & Clark, L. (2015). Risk-sensitive decision-making in patients with posterior parietal and ventromedial prefrontal cortex injury. Cerebral Cortex, 25, 1–9.

Studte, S., Bridger, E., & Mecklinger, A. (2015). Nap sleep preserves associative but not item memory preference. Neurobiology of Learning and Memory, 120, 84–93.

Suchan, B., Bauser, D. S., Busch, M., Schulte, D., Grönemeyer, D., Herpetz, S., & Vocks, S. (2013). Reduced connectivity between the left fusiform body area and the extrastriate body area in anorexia nervosa is associated with body image distortion. Behavioural Brain Research, 241, 80–85.

Suddath, R. L., Casanova, M. F., Goldberg, T. E., Daniel, D. G., Kelsoe, J. R., & Weinberger, D. R. (1989). Temporal lobe pathology in schizophrenia: A quantitative magnetic resonance imaging study. American Journal of Psychiatry, 146, 464–472.

Suddath, R. L., Christison, G. W., Torrey, E. F., Casanova, M. F., & Weinberger, D. R. (1990). Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. New England Journal of Medicine, 322, 789–794.

Sullivan, P. F. (1995). Mortality in anorexia nervosa. American Journal of Psychiatry, 152, 1073–1074.

Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. Archives of General Psychiatry, 60, 1187–1192.

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression. American Journal of Psychiatry, 157, 1552–1562.

Sun, X., Tang, M., Zhang, J., & Chen, J. D. Z. (2006). Excitatory effects of gastric electrical stimulation on gastric distension responsive neurons in ventromedial hypothalamus (VMH) in rats. Neuroscience Research, 16, 344–352.

Supa, M., Cotzin, M., & Dallenbach, K. M. (1944). “Facial vision”: The perception of obstacles by the blind. American Journal of Psychology, 57, 133–183.

Surat, P. (n.d.). Applications of CLARITY. News Life Sciences. Retrieved from https://www.news-medical.net/life-sciences/Applications-of-CLARITY.aspx

Surén, P., Roth, C., Bresnahan, M., Haugen, M., Hornig, M., Hirtz, D., et al. (2013). Association between maternal use of folic acid supplements and risk of autism in children. Journal of the American Medical Association, 309, 570–577.

Susser, E., Neugebauer, R., Hoek, H. W., Brown, A. S., Lin, S., Labovitz, D., et al. (1996). Schizophrenia after prenatal famine: Further evidence. Archives of General Psychiatry, 53, 25–31.

Sutin, A. R., Zonderman, A. B., Ferrucci, L., & Terracciano, A. (2013). Personality traits and chronic disease: Implications for adult personality development. Journals of Gerontology, Series B: Psychological Sciences and Social Sciences, 68, 912–920.

Suvisaari, J. M., Haukka, J. K., Tanskanen, A. J., & Lönnqvist, J. K. (1999). Decline in the incidence of schizophrenia in Finnish cohorts born from 1954 to 1965. Archives of General Psychiatry, 56, 733–740.

Suzdak, P. D., Glowa, J. R., Crawley, J. N., Schwartz, R. D., Skolnick, P., & Paul, S. M. (1986). A selective imidazobenzodiazepine antagonist of ethanol in the rat. Science, 234, 1243–1247.

Suzuki, A., Stem, S. A., Bozdagi, O., Huntley, G. W., Walker, R. H., Magistretti, P. J., & Alberini, C. M. (2011). Astrocyte-neuron lactate transport is required for long-term memory formation. Cell, 144, 810–823.

Svensson, T. H., Grenhoff, J., & Aston-Jones, G. (1986). Midbrain dopamine neurons: Nicotinic control of firing pattern. Society for Neuroscience Abstracts, 12, 1154.

Swaab, D. F. (1996). Desirable biology. Science, 382, 682–683.

Swaab, D. F., & Hofman, M. A. (1990). An enlarged suprachiasmatic nucleus in homosexual men. Brain Research, 537, 141–148.

Swaab, D. F., Slob, A. K., Houtsmuller, E. J., Brand, T., & Zhou, J. N. (1995). Increased number of vasopressin neurons in the

suprachiasmatic nucleus (SCN) of “bisexual” adult male rats following perinatal treatment with the aromatase blocker ATD. Developmental Brain Research, 85, 273–279.

Swanson, L. W. (1982). The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Research Bulletin, 9, 321–353.

Swedo, S. E., Rapoport, J. L., Leonard, H. L., Lenane, M., & Cheslow, D. (1989). Obsessive-compulsive disorder in children and adolescents: Clinical phenomenology of 70 consecutive cases. Archives of General Psychiatry, 46, 335–341.

Swedo, S. E., Rapoport, J. L., Leonard, H. L., Schapiro, M. B., Rapoport, S. I., & Grady, C. L. (1991). Regional cerebral glucose metabolism of women with trichotillomania. Archives of General Psychiatry, 48, 828–833.

Swedo, S. E., Schapiro, M. B., Grady, C. L., Cheslow, D. L., Leonard, H. L., Kumar, A., et al. (1989). Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Archives of General Psychiatry, 46, 518–523.

Sylvester, C. M., Corbetta, M., Raichle, M. E., Rodebaugh, T. L., Schlaggar, B. L., Sheline, Y. I., et al. (2012). Functional network dysfunction in anxiety and anxiety disorders. Trends in Neurosciences, 35, 527–535.

Szalavitz, M. (2000). Drugs to fight drugs. HMS Beagle. Retrieved from http://www.news.bmn.com/hmsbeagle/91/notes/feature1

Szeszko, P. R., Ardekani, B. A., Ashtari, M., Malhotra, A. K., Robinson, D. G., Bilder, R. M., et al. (2005). White matter abnormalities in obsessive-compulsive disorder: A diffusion tensor imaging study. Archives of General Psychiatry, 62, 782–790.

Tabrizi, S. J., Cleeter, M. W., Xuereb, J., Taanman, J. W., Cooper, J. M., & Schapira, A. H. (1999). Biochemical abnormalities and excitotoxicity in Huntington's disease brain. Annals of Neurology, 45, 25–32.

Tadic, A., Rujescu, D., Szegedi, A., Giegling, I., Singer, P., Möller, H.-J., et al. (2003). Association of a *MAOA* gene variant with generalized anxiety disorder, but not with panic disorder or major depression. American Journal of Medical Genetics Part B, 117B, 1–6.

Takayanagi, Y., Spira, A. P., Roth, K. B., Gallo, J. J., Eaton, W. W., & Mojtabai, R. (2014). Accuracy of reports of lifetime medical and physical disorders: Results from the Baltimore epidemiological catchment area study. JAMA Psychiatry, 71(3), 273–280.

Talaei, A., Pourgholami, M., Khatibi-Moghadam, H., Faridhosseini, F., Farhoudi, F., Askari-Noghani, A., & Sadeghi, R. (2016). Tamoxifen: A protein kinase C inhibitor to treat mania: A systematic review and meta-analysis of randomized, placebo-controlled trials. Journal of Clinical Psychopharmacology, 36, 272–275.

Tam, N., & Noakes, T. D. (2013). The quantification of body fluid allostasis during exercise. Sports Medicine, 43, 1289–1299.

Tamietto, M., Castelli, L., Vighetti, S., Perozzo, P., Geminiani, G., Weiskrantz, L., et al. (2009). Unseen facial and bodily expressions trigger fast emotional reactions. Proceedings of the National Academy of Sciences, 106, 17661–17666.

Tamietto, M., Cauda, F., Corazzini, L. L., Savazzi, S., Marzi, C. A., Goebel, R., et al. (2010). Collicular vision guides nonconscious behavior. Journal of Cognitive Neuroscience, 22, 888–902.

Tanaka, K. (1996). Inferotemporal cortex and object vision. Annual Review of Neuroscience, 19, 109–139.

Tanaka, K. (2003). Columns for complex visual object features in the inferotemporal cortex: Clustering of cells with similar but slightly different stimulus selectivities. Cerebral Cortex, 13, 90–99.

Tanda, G., Munzar, P., & Goldberg, S. R. (2000). Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. Nature Neuroscience, 3, 1073–1074.

Tanji, J., & Shima, K. (1994). Role for supplementary motor area cells in planning several movements ahead. Nature, 371, 413–416.

Tanner, C. M., Ottman, R., Goldman, S. M., Ellenberg, J., Chan, P., Mayeux, R., et al. (1999). Parkinson disease in twins: An etiologic study. Journal of the American Medical Association, 281, 341–346.

Taylor, D. J. (2008). Insomnia and depression. Sleep, 31, 447–448.

Taylor, D. N. (1995). Effects of a behavioral stress-management program on anxiety, mood, self-esteem, and T-cell count in HIV-positive men. Psychological Reports, 76, 451–457.

Taylor, L. E., Swerdfeger, A. L., & Eslick, G. D. (2014). Vaccines are not associated with autism: An evidence-based meta-analysis of case-control and cohort studies. Vaccine, 32, 3623–3629.

Taylor, R. C. (2017). Sensory biology: How female treefrogs pick mates at a noisy party. Current Biology, 27, R188–R190.

Taylor, S. (2013). Molecular genetics of obsessive-compulsive disorder: A comprehensive meta-analysis of genetic association studies. Molecular Psychiatry, 18, 799–805.

Taylor, V. H., Curtis, C. M., & Davis, C. (2009). The obesity epidemic: The role of addiction. Canadian Medical Association Journal, 182(4), 327–238. doi:10.1503/cmaj.091142

Telzer, E. H., Ichien, N. T., & Qu, Y. (2015). Mothers know best: Redirecting adolescent reward sensitivity toward safe behavior during risk taking. Social Cognitive and Affective Neuroscience, 10, 1383–1391.

Tepas, D. I., & Carvalhais, A. B. (1990). Sleep patterns of shiftworkers. Occupational Medicine, 5, 199–208.

Terrace, H. S., Petitto, L. A., Sanders, R. J., & Bever, T. G. (1979). Can an ape create a sentence? Science, 206, 891–901.

Terribile, M., Stizzo, M., Manfredi, C., Quattrone, C., Bottone, F., Giordano, D. R., et al. (2019). 46,XX testicular disorder of sex development (DSD): A case report and systematic review. Medicina, 55, 371. Retrieved from https://www.mdpi.com/1010-660X/55/7/371

Tessier-Lavigne, M., & Goodman, C. S. (1996). The molecular biology of axon guidance. Science, 274, 1123–1132.

Tessmar-Raible, K., Raible, F., & Arboleda, E. (2011). Another place, another timer: Marine species and the rhythms of life. Bioessays, 33, 165–172.

Thaler, L., Arnott, S. R., & Goodale, M. A. (2011). Neural correlates of natural human echolocation in early and late blind echolocation experts. PLoS ONE, 6, e20162. doi:10.1371/journal.pone.0020162

Thaler, L., Reich, G. M., Zhang, X., Wang, D., Smith, G. E., Tao, Z., et al. (2017). Mouth-clicks used by blind expert human echolocators—Signal description and model based signal

synthesis. PLoS Computational Biology, 13(8), e1005670. Retrieved from https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1005670

Thallmair, M., Metz, G. A. S., Z'Graggen, W. J., Raineteau, O., Kartje, G. L., & Schwab, M. E. (1998). Neurite growth inhibitors restrict plasticity and functional recovery following corticospinal tract lesions. Nature Neuroscience, 1(2), 124–131.

Thambisetty, M., Beason-Held, L., An, Y., Kraut, M. A., & Resnick, S. M. (2010). *APOE ε4* genotype and longitudinal changes in cerebral blood flow in normal aging. Archives of Neurology, 67, 93–98.

Therrell, B. L. (2001). Newborn screening for congenital adrenal hyperplasia. Endocrinology & Metabolism Clinics of North America, 30, 15–30.

Thibaut, F., Cordier, B., & Kuhn, J.-M. (1996). Gonadotrophin hormone releasing hormone agonist in cases of severe paraphilia: A lifetime treatment? Psychoneuroendocrinology, 21, 411–419.

Thiele, A., Henning, P., Kubischik, M., & Hoffmann, K.-P. (2002). Neural mechanisms of saccadic suppression. Science, 295, 2460–2462.

Thier, P., Haarmeier, T., Chakraborty, S., Lindner, A., & Tikhonov, A. (2001). Cortical substrates of perceptual stability during eye movements. NeuroImage, 14, S33–S39.

Thigpen, C. H., & Cleckley, H. M. (1957). The three faces of Eve. London, UK: Secker & Warburg.

Thomas, R., Sanders, S., Doust, J., Beller, E., & Glasziou, P. (2015). Prevalence of attention-deficit/hyperactivity disorder: A systematic

review and meta-analysis. Pediatrics, 135, e994–e1001. doi:10.1542/peds2014-3482

Thompson, P. M., Cannon, T. D., Narr, K. L., van Erp, T., Poutanen, V.-P., Huttunen, M., et al. (2001). Genetic influences on brain structure. Nature Neuroscience, 4, 1253–1258.

Thompson, P. M., Hayashi, K. M., Simon, S. L., Geaga, J. A., Hong, M. S., Sui, Y., et al. (2004). Structural abnormalities in the brains of human subjects who use methamphetamine. Journal of Neuroscience, 24, 6028–6036.

Thompson, P. M., Vidal, C., Giedd, J. N., Gochman, P., Blumenthal, J., Nicolson, R., et al. (2001). Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. Proceedings of the National Academy of Sciences, 98, 11650–11655.

Thomson, H. (2018, May 23). Minimally conscious people woken with brain zap by their family. New Scientist. Retrieved from https://www.newscientist.com/article/mg23831793-200-minimally-conscious-people-woken-with-brain-zap-by-their-family

Thomson, S. N., Avidan, N., Lee, K., Sarma, A. K., Tushe, R., Milewicz, D. M., et al. (2011). The genetics of colored sequence synesthesia: Suggestive evidence of linkage to 16q and genetic heterogeneity for the condition. Behavioural Brain Research, 223, 48–52.

Thornton, L. M., Mazzeo, S. E., & Bulik, C. M. (2011). The heritability of eating disorders: methods and current findings. Current Topics in Behavioral Neuroscience. 6, 141–156.

Thyme, S. B., Pieper, L. M., Li, E. H., Pandey, S., Wang, Y., Morris, N. S., et al. (2019). Phenotypic landscape of schizophrenia-

associated genes defines candidates and their shared functions. Cell, 177, 478–491.

Tobi, E. W., Lumey, L. H., Talens, R. P., Kremer, D., Putter, H., Stein, A. D., et al. (2009). DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. Human Molecular Genetics, 18, 4046–4053.

Tobi, E. W., Slagboom, P. E., van Dongen, J., Kremer, D., Stein, A. D., Putter, H., et al. (2012). Prenatal famine and genetic variation are independently and additively associated with DNA methylation at regulatory loci within IGF2/H19. PLoS One, 7, e37933. Retrieved from http://www.plosone.org/article/info%3A-doi%2F10.1371%2Fjournal.pone.0037933

Toda, M., & Abi-Dargham, A. (2007). Dopamine hypothesis of schizophrenia: Making sense of it all. Current Psychiatry Reports, 9, 329–336.

Tohen, M. (2015). Cariprazine in bipolar disorders. Journal of Clinical Psychiatry, 73(3), e368–e370.

Tolin, D. F., Stevens, M. C., Villavicencio, A. L., Norberg, M. M., Calhoun, V. D., Frost, R. O., et al. (2012). Neural mechanisms of decision making in hoarding behavior. Archives of General Psychiatry, 69, 832–841.

Tomer, R., Ye, L., Hsueh, B., & Deisseroth, K. (2014). Advanced CLARITY for rapid and high-resolution imaging of intact tissues. Nature Protocols, 9, 1682–1697. doi:10.1038/nprot.2014.123

Tong, F. (2003). Primary visual cortex and visual awareness. Nature Reviews Neuroscience, 4, 219–229.

Toni, N., Buchs, P.-A., Nikonenko, I., Bron, C. R., & Muller, D. (1999). LTP promotes formation of multiple spine synapses between a single axon terminal and a dendrite. Nature, 402, 421–425.

Tononi, G. (2005). Consciousness, information integration, and the brain. In S. Laureys (Ed.), The boundaries of consciousness: Neurobiology and neuropathology (pp. 109–126). New York, NY: Elsevier.

Tononi, G. (2008). Consciousness as integrated information: A provisional manifesto. Biological Bulletin, 215, 216–242.

Tononi, G., & Cirelli, C. (2013). Perchance to prune. Scientific American, 309, 34–39.

Tononi, G., & Cirelli, C. (2014). Sleep and the price of plasticity: From synaptic and cellular homeostasis to memory consolidation and integration. Cell, 81, 1–34.

Tootell, R. B. H., Silverman, M. S., Switkes, E., & De Valois, R. L. (1982). Deoxyglucose analysis of retinotopic organization in primate striate cortex. Science, 218, 902–904.

Topol, A., Zhu, S., Hartley, B. J., English, J., Hauberg, M. E., Tran, N., et al. (2016). Dysregulation of miRNA-9 in a subset of schizophrenia patient-derived neural progenitor cells. Cell Reports, 15, 1024–1036.

Torgerson, C. M., Irimia, A., Goh, S. Y. M., & Van Horn, J. D. (2015). The DTI connectivity of the human claustrum. Human Brain Mapping, 36, 827–838.

Torii, M., Hashimoto-Torii, K., Levitt, P., & Rakic, P. (2009). Integration of neuronal clones in the radial cortical columns by EphA and ephrin-A signalling. Nature, 461, 524–530.

Toshitani, K., Kobayashi, T., Osawa, T., Kato, S., Eto, S., & Ojima, T. (2006). Is the incidence of schizophrenia declining? An investigation of the examination rates in the psychiatric clinics of a medical school hospital and a general hospital. Seishin shinkeigaku zasshi, 108, 694–704.

Touhara, K., & Vosshall, L. B. (2009). Sensing odorants and pheromones with chemosensory receptors. Annual Review of Physiology, 71, 307–332.

Townsend, J., Courchesne, E., Covington, J., Westerfield, M., Harris, N. S., Lyden, P., et al. (1999). Spatial attention deficits in patients with acquired or developmental cerebellar abnormality. Journal of Neuroscience, 19, 5632–5643.

Trace, S. E., Baker, J. H., Peñas-Lledó, E., & Bulik, C. M. (2013). The genetics of eating disorders. Annual Review of Clinical Psychology, 9, 589–620.

Tracey, I., Ploghaus, A., Gati, J. S., Clare, S., Smith, S., Menon, R. S., et al. (2002). Imaging attentional modulation of pain in the periaqueductal gray in humans. Journal of Neuroscience, 22, 2748–2752.

Tracy, T. E., Sohn, P. D., Minami, S. S., Wang, C., Min, S. W., Li, Y., et al. (2016). Acetylated tau obstructs KIBRA-mediated signaling in synaptic plasticity and promotes tauopathy-related memory loss. Neuron, 90, 245–260.

Traish, A. M. (2017). Negative impact of testosterone deficiency and 5∝-reductase inhibitors therapy on metabolic and sexual function in men. Advances in Experimental Medicine and Biology, 1043, 473–526.

Tranel, D., & Damasio, A. R. (1985). Knowledge without awareness: An autonomic index of facial recognition by prosopagnosics.

Science, 228, 1453–1454.

Tranel, D., Damasio, A. R., & Damasio, H. (1988). Intact recognition of facial expression, gender, and age in patients with impaired recognition of face identity. Neurology, 38, 690–696.

Träskman, L., Åsberg, M., Bertilsson, L., & Sjöstrand, L. (1981). Monoamine metabolites in CSF and suicidal behavior. Archives of General Psychiatry, 38, 631–635.

Trautmann, A. (1983). Tubocurarine, a partial agonist for cholinergic receptors. Journal of Neural Transmission. Supplementum, 18, 353–361.

Trautmann, S., Rehm, J., & Wittchen, H. (2016). The economic costs of mental disorders. EMBO Reports, 17, 1245–1249.

Treffert, D. A., & Christensen, D. D. (2006, June/July). Inside the mind of a savant. Scientific American Mind, 17, 50–55.

Tregellas, J. R., Tanabe, J. L., Martin, L. F., & Freedman, R. (2005). fMRI of response to nicotine during a smooth pursuit eye movement task in schizophrenia. American Journal of Psychiatry, 162, 391–393.

Treger, J. (2015). Single-molecule fluorimetry and gating currents inspire an improved optical voltage indicator. eLife, 4, e10482. doi:10.7554/eLife.10482

Trepanowski, J. F., Canale, R. E., Marshall, K. E., Kabir, M. M., & Bloomer, R. J. (2011). Impact of caloric and dietary restriction regimens on markers of health and longevity in humans and animals: A summary of available findings. Nutrition Journal, 10, 107. Retrieved from http://www.nutritionj.com/content/10/1/107

Tripp, G., & Wickens, J. R. (2009). Neurobiology of ADHD. Neuropharmacology, 57, 579–589.

Trudeau, L.-É. (2004). Glutamate co-transmission as an emerging concept in monoamine neuron function. Reviews in Psychiatric Neuroscience, 29, 296–310.

Trulson, M. E., Crisp, T., & Trulson, V. M. (1984). Activity of serotonin-containing nucleus centralis superior (raphe medianus) neurons in freely moving cats. Experimental Brain Research, 54, 33–44.

Tsai, G., Gastfriend, D. R., & Coyle, J. T. (1995). The glutamatergic basis of human alcoholism. American Journal of Psychiatry, 152, 332–340.

Tsai, S.-J., Hong, C.-J., & Liou, Y.-J. (2011). Recent molecular genetic studies and methodological issues in suicide research. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 35, 809–817.

Tsankova, N., Renthal, W., Kumar, A., & Nestler, E. J. (2007). Epigenetic regulation in psychiatric disorders. Nature Reviews Neuroscience, 8, 355–367.

Tsend-Ayush, E., He, C., Myers, M. A., Andrikopoulos, S., Wong, N., Sexton, P. M., et al. (2016). Monotreme *glucagon-like peptide-1* in venom and gut: One gene—two very different functions. Scientific Reports, 6, 37744. doi:10.1038/srep37744

Tsuang, M. T., Gilbertson, M. W., & Faraone, S. V. (1991). The genetics of schizophrenia: Current knowledge and future directions. Schizophrenia Research, 4, 157–171.

Tsujino, N., & Sakurai, T. (2009). Orexin/hypocretin: A neuropeptide at the interface of sleep, energy homeostasis, and reward system. Pharmacological Reviews, 61, 162–176.

Tuiten, A., Van Honk, J., Koppeschaar, H., Bernaards, C., Thijssen, J., & Verbaten, R. (2000). Time course of effects of testosterone administration on sexual arousal in women. Archives of General Psychiatry, 57, 149–153.

Tun, H. M., Konya, T., Takaro, T. K., Brook, J. R., Chari, R., Field, C. J., et al. (2017). Exposure to household furry pets influences the gut microbiota of infants at 3–4 months following various birth scenarios. Microbiome, 5, 40–54. doi:10.1186/s40168-017-0254-x

Turban, J. L., Beckwith, N., Reisner, S. L., & Keuroghlian, A. S. (2020). Association between recalled exposure to gender identity conversion efforts and psychological distress and suicide attempts among transgender adults. JAMA Psychiatry, 77, 68.

Turkheimer, E. (1991). Individual and group differences in adoption studies of IQ. Psychological Bulletin, 110, 392–405.

Turner, M. S., Cipolotti, L., Yousry, T. A., & Shallice, T. (2008). Confabulation: Damage to a specific inferior medial prefrontal system. Cortex, 44, 637–648.

Tuvblad, C., & Baker, L. A. (2011). Human aggression across the lifespan: Genetic propensities and environmental moderators. Advances in Genetics, 75, 171–214.

Twenge, J. M., Sherman, R. A., & Wells, B. E. (2016). Changes in American adults' reported same-sex sexual experiences and attitudes, 1973–2014. Archives of Sexual Behavior, 45, 1713–1730.

Twiss, K. C. (2019). The archaeology of food: Identity, politics, and ideology in the prehistoric and historic past. Cambridge, UK: Cambridge University Press.

Uchino, B. N., Vaughn, A. A., Carlisle, M., & Birmingham, W. (2012). Social support and immunity. In S. Segerstrom (Ed.), Oxford handbook of psychoneuroimmunology (pp. 214–233). New York, NY: Oxford University Press.

Uddin, L. O., (2015). Salience processing and insular cortical function and dysfunction. Nature Reviews Neuroscience, 16, 55–61.

Uhl, G. R., & Grow, R. W. (2004). The burden of complex genetics in brain disorders. Archives of General Psychiatry, 61, 223–229.

Uhlhaas, P. J., & Singer, W. (2010). Abnormal neural oscillations and synchrony in schizophrenia. Nature Reviews Neuroscience, 11, 100–113.

Ujike, H., Otani, K., Nakatsuka, M., Ishii, K., Sasaki, A., Oishi, T., et al. (2009). Association study of gender identity disorder and sex hormone-related genes. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 33, 1241–1244.

Ulanovsky, N., & Moss, C. F. (2008). What the bat's voice tells the bat's brain. Proceedings of the National Academy of Sciences, 105(25), 8491–8498.

Ullian, E. M., Sapperstein, S. K., Christopherson, K. S., & Barres, B. A. (2001). Control of synapse number by glia. Science, 291, 657–660.

Ullman, M. T. (2001). A neurocognitive perspective on language: The declarative/procedural model. Nature Reviews Neuroscience, 2,

717–726.

Uncapher, M. R., Otten, L. J., & Rugg, M. D. (2006). Episodic encoding is more than the sum of its parts: An fMRI investigation of multifeatural contextual encoding. Neuron, 52, 547–556.

Ungerleider, L. G., & Haxby, J. V. (1994). “What” and “where” in the human brain. Current Opinion in Neurobiology, 4, 157–165.

Ungerleider, L. G., & Mishkin, M. (1982). Two cortical visual systems. In D. J. Ingle, M. A. Goodale, & R. J. W. Mansfield (Eds.), Analysis of visual behavior (pp. 549–586). Cambridge, MA: MIT Press.

United Nations Office on Drugs and Crime. (2019). Global study on homicide. Retrieved from https://dataunodc.un.org/GSH_app

U.S. Burden of Disease Collaborators. (2013). The state of US health, 1990–2010: Burden of diseases, injuries, and risk factors. Journal of the American Medical Association, 310, 591–608.

U.S. Congress Office of Technology Assessment. (1986). Alternatives to animal research in testing and education. Washington, DC: U.S. Government Printing Office.

U.S. Department of Health and Human Services. (2012). Overweight and obesity statistics. Retrieved from http://win.niddk.nih.gov/publications/PDFs/stat904z.pdf

U.S. Environmental Protection Agency. (2019, September 10). Administrator Wheeler signs memo to reduce animal testing, awards $4.25million to advance research on alternative methods to animal testing. Retrieved from https://www.epa.gov/newsreleases/administrator-wheeler-signs-memo-reduce-animal-testing-awards-425-million-advance

U.S. Food and Drug Administration. (2003, October 17). FDA approves memantine (Namenda) for Alzheimer's disease. Retrieved from http://www.fda.gov/bbs/topics/NEWS/2003/NEW00961.html

U.S. Food and Drug Administration. (2009). FDA approves humanitarian device exemption for deep brain stimulator for severe obsessive-compulsive disorder. Retrieved from http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149529.htm

U.S. Food and Drug Administration. (2012, July 2). FDA drug safety communication: Seizure risk for multiple sclerosis patients who take Ampyra (dalfampridine). Retrieved from http://www.fda.gov/Drugs/DrugSafety/ucm312846.htm

U.S. Food and Drug Administration. (2017, November 15). FDA grants marketing authorization of the first device for use in helping to reduce the symptoms of opioid withdrawal. FDA News Release. Retrieved from https://www.fda.gov/news-events/press-announcements/fda-grants-marketing-authorization-first-device-use-helping-reduce-symptoms-opioid-withdrawal

U.S. Food and Drug Administration. (2019, August 27). FDA approves new add-on drug to treat off episodes in adults with Parkinson's disease. FDA News Release. Retrieved from https://www.fda.gov/news-events/press-announcements/fda-approves-new-add-drug-treat-episodes-adults-parkinsons-disease

U.S. government shuts down Pennsylvania gene therapy trials. (2000). Nature, 403, 354–355.

Vaaga, C. E., Borisovska, M., & Westbrook, G. L. (2014). Dual-transmitter neurons: Functional implications of co-release and co-transmission. Current Opinion in Neurobiology, 29, 25–32.

Vagell, M. E., & McGinnis, M. Y. (1997). The role of aromatization in the restoration of male rat reproductive behavior. Journal of Neuroendocrinology, 9, 415–421.

Vaina, L. M. (1998). Complex motion perception and its deficits. Current Opinion in Neurobiology, 8, 494–502.

Vaina, L. M., Solomon, J., Chowdhury, S., Sinha, P., & Belliveau, J. W. (2001). Functional neuroanatomy of biological motion perception in humans. Proceedings of the National Academy of Sciences, 98, 11656–11661.

Vainik, U., Baker, T. E., Dadar, M., Zeighami, Y., Michaud, A., Zhang, Y., et al. (2018). Neurobehavioral correlates of obesity are largely heritable. Proceedings of the National Academy of Sciences, 115, 9312–9317.

Vaisvaser, S., Modai, S., Farberov, L, Lin, T., Sharon, H., Gilam, A., et al. (2016). Neuro-epigenetic indications of acute stress response in humans: The case of microRNA-29c. PLoS One, 11(1), e0146236. Retrieved from https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0146236

Valenstein, E. S. (1986). Great and desperate cures. New York, NY: Basic Books.

van Anders, S. M., Goldey, K. L., & Kuo, P. X. (2011). The steroid/peptide theory of social bonds: Integrating testosterone and peptide responses for clarifying social behavioral contexts. Psychoneuroendocrinology, 36, 1265–1275.

van den Brand, R., Heutschi, J., Barraud, Q., DiGiovanna, J., Bartholdi, K., Huerlimann, M., et al. (2012). Restoring voluntary control of locomotion after paralyzing spinal cord injury. Science, 336, 1182–1185.

van der Veen, F. M., Nijhuis, F. A. P., Tisserand, D. J., Backes, W. H., & Jolles, J. (2006). Effects of aging on recognition of intentionally and incidentally stored words: An fMRI study. Neuropsychologia, 44, 2477–2486.

Van Dongen, H. P. A., Maislin, G., Mullington, J. M., & Dinges, D. F. (2003). The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep, 26, 117–126.

Van Essen, D. C., Anderson, C. H., & Felleman, D. J. (1992). Information processing in the primate visual system: An integrated systems perspective. Science, 255, 419–423.

Van Essen, D. C., Smith, S. M., Barch, D. M., Behrens, T. E. J., Yacoub, E., Ugurbil, K., et al. (2013). The WU-Minn Human Connectome Project: An overview. NeuroImage, 62, 2222–2231.

Van Horn, J. D. (2019). What is old is new again: Investigating and analyzing the mysteries of the claustrum. Neuroinformatics, 17, 1–3.

Van Horn, J. D., Irimia, A., Torgerson, C. M., Chambers, M. C., Kikinis, R., & Toga, A. W. (2012). Mapping connectivity damage in the case of Phineas Gage. PLoS One, 7, e37454. doi:10.1371/journal.pone.0037454

van Meer, G., Voelker, D. R., & Feigenson, G. W. (2008). Membrane lipids: Where they are and how they behave. Nature Reviews: Molecular Cell Biology, 9, 112–124.

van Os, J., & Selten, J. (1998). Prenatal exposure to maternal stress and subsequent schizophrenia: The May 1940 invasion of the Netherlands. British Journal of Psychiatry, 172, 324–326.

Van Wyk, P. H., & Geist, C. S. (1984). Psychosocial development of heterosexual, bisexual, and homosexual behavior. Archives of Sexual Behavior, 13, 505–544.

Vargha-Khadem, F., Gadian, D. G., Copp, A., & Mishkin, M. (2005). *FOXP2* and the neuroanatomy of speech and language. Nature Reviews Neuroscience, 6, 131–138.

Vauzour, D. (2014). Effect of flavonoids on learning, memory and neurocognitive performance: Relevance and potential implications for Alzheimer's disease pathophysiology. Journal of the Science of Food and Agriculture, 94(6), 1042–1056.

Veitia, R., Ion, A., Barbaux, S., Jobling, M. A., Souleyreau, N., Ennis, K., et al. (1997). Mutations and sequence variants in the testis-determining region of the Y chromosome in individuals with a 46,XY female phenotype. Human Genetics, 99, 648–652.

Venter, J. C. (and 273 others). (2001). The sequence of the human genome. Science, 291, 1304–1351.

Verbalis, J. G. (2007). How does the brain sense osmolality? Journal of the American Society of Nephrology, 18, 3056–3059.

Verbene, A. J. M., Sabetghadam, A., & Korim, W. S. (2014). Neural pathways that control the glucose counterregulatory response. Frontiers in Neuroscience, 8, Article 38. doi:10.3389/fnins.2014.00038

Vermetten, E., Schmahl, C., Lindner, S., Loewenstein, R. J., & Bremner, J. D. (2006). Hippocampal and amygdalar volumes in dissociative identity disorder. American Journal of Psychiatry, 163, 630–636.

Vernes, S. C., Newbury, D. F., Abrahams, B. S., Winchester, L., Nicod, J., Groszer, M., et al. (2008). A functional genetic link between distinct developmental language disorders. New England Journal of Medicine, 359, 2337–2345.

Veroude, K., Zhang-James, Y., Fernàndez-Castillo, N., Bakker, M. J., Cormand, B., & Faraone, S. V. (2016). Genetics of aggressive behavior: An overview. American Journal of Medical Genetics Part B, 171B, 3–43.

Vgontzas, A. N., Bixler, E. O., Lin, H. M., Prolo, P., Mastorakos, G., Vela-Bueno, A., et al. (2001). Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: Clinical implications. Journal of Clinical Endocrinology and Metabolism, 86, 3787–3794.

Vikingstad, E. M., Cao, Y., Thomas, A. J., Johnson, A., Malik, G. M., & Welch, K. M. A. (2000). Language hemispheric dominance in patients with congenital lesions of eloquent brain. Neurosurgery, 47, 562–570.

Villafuerte, S., Heitzeg, M. M., Foley, S., Yau, W.-Y., Majczenko, K., Zubieta, J.-K., et al. (2012). Impulsiveness and insula activation during reward anticipation are associated with genetic variants in GABRA2 in a family sample enriched for alcoholism. Molecular Psychiatry, 17, 511–519.

Villalobos, M. E., Mizuno, A., Dahl, B. C., Kemmotsu, N., & Müller, R.-A. (2005). Reduced functional connectivity between V1 and inferior frontal cortex associated with visuomotor performance in autism. NeuroImage, 25, 916–925.

Virkkunen, M., Goldman, D., & Linnoila, M. (1996). Serotonin in alcoholic violent offenders. In G. R. Bock & J. A. Goode (Ed.), Genetics of criminal and antisocial behaviour. Ciba Foundation Symposium 194 (pp. 168–182). Chichester, UK: Wiley.

Virkkunen, M., & Linnoila, M. (1993). Brain serotonin, Type II alcoholism and impulsive violence. Journal of Studies of Alcohol Supplement, 11, 163–169.

Visser, S. N., Danielson, M. L., Bitsko, R. H., Holbrook, J. R., Kogan, M. D., Ghandour, R. M., et al. (2014). Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003–2011. Journal of the American Academy of Child & Adolescent Psychiatry, 53, 34–46.

Vissers, L. E. L. M., Gilissen, C., & Veltman, J. A. (2016). Genetic studies in intellectual disability and related disorders. Nature Reviews Genetics, 17, 9–18.

Vogel, G. (1998). Penetrating insight into the brain. Science, 282, 39.

Vogel, G. W., Buffenstein, A., Minter, K., & Hennessey, A. (1990). Drug effects on REM sleep and on endogenous depression. Neuroscience and Biobehavioral Review, 14, 49–63.

Vogels, R. (1999). Categorization of complex visual images by rhesus monkeys: Part 2. Single-cell study. European Journal of Neuroscience, 11, 1239–1255.

Voineagu, I., Wang, X., Johnston, P., Lowe, J. K., Tian, Y., Horvath, S., et al. (2011). Transcriptomic analysis of autistic brain reveals convergent molecular pathology. Nature, 474, 380–386.

Volk, H. E., Lurmann, F., Penfold, B., Hertz-Picciotto, I., & McConnell, R. (2014). Traffic-related air pollution, particulate matter, and autism. JAMA Psychiatry, 70, 71–77.

Volkow, N. D., Fowler, J. S., & Wang, G.-J. (2004). The addicted human brain viewed in the light of imaging studies: Brain circuits

and treatment strategies. Neuropharmacology, 47(Suppl.), 3–13.

Volkow, N. D., Fowler, J. S., Wang, G.-J., & Swanson, J. M. (2004). Dopamine in drug abuse and addiction: Results from imaging studies and treatment implications. Molecular Psychiatry, 9, 557–569.

Volkow, N. D., Fowler, J. S., Wolf, A. P., Hitzemann, R., Dewey, S., Bendriem, B., et al. (1991). Changes in brain glucose metabolism in cocaine dependence and withdrawal. American Journal of Psychiatry, 148, 621–626.

Volkow, N. D., Wang, G.-J., Fowler, J. S., Hitzemann, R., Angrist, B., Gatley, S. J., et al. (1999). Association of methylphenidate-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers: Implications in addiction. American Journal of Psychiatry, 156, 19–26.

Volkow, N. D., Wang, G.-J., Tomasi, D., & Baler, R. D. (2013). The addictive dimensionality of obesity. Biological Psychiatry, 73, 811–818.

Volkow, N. D., & Wise, R. A. (2005). How can drug addiction help us understand obesity? Nature Neuroscience, 8, 555–560.

von Bartheld, C. S., Bahney, J., & Herculano-Houzel, S. (2016). The search for true numbers of neurons and glial cells in the human brain: A review of 150 years of cell counting. Journal of Comparative Neurology, 15, 3865–3895.

von der Heydt, R., Peterhans, E., & Baumgartner, G. (1984). Illusory contours and cortical neuron responses. Science, 224, 1260–1262.

von der Heydt, R., Peterhans, E., & Dürsteler, M. R. (1992). Periodic pattern-selective cells in monkey visual cortex. Journal of Neuroscience, 12, 1416–1434.

Vorel, S. R., Liu, X., Hayes, R. J., Spector, J. A., & Gardner, E. L. (2001). Relapse to cocaine-seeking after hippocampal theta burst stimulation. Science, 292, 1175–1178.

Voyer, D., Voyer, S., & Bryden, M. P. (1995). Magnitude of sex differences in spatial abilities: A meta-analysis and consideration of critical variables. Psychological Bulletin, 117, 250–270.

Vu, E. T., Mazurek, M. E., & Kuo, Y.-C. (1994). Identification of a forebrain motor programming network for the learned song of zebra finches. Journal of Neuroscience, 14(11), 6924–6934.

Vul, E., Harris, C., Winkielman, P., & Pashler, H. (2009). Puzzlingly high correlations in fMRI studies of emotion, personality, and social cognition. Perspectives on Psychological Science, 4, 274–290.

Wada, J. A., Clarke, R., & Hamm, A. (1975). Cerebral hemispheric asymmetry in humans: Cortical speech zones in 100 adult and 100 infant brains. Archives of Neurology, 32, 239–246.

Wade, J. A., Garry, M., Read, J. D., & Lindsay, S. (2002). A picture is worth a thousand lies. Psychonomic Bulletin Reviews, 9, 597–603.

Wagner, D., Becker, B., Koester, P., Gouzoulis-Mayfrank, E., & Daumann, J. (2013). A prospective study of learning, memory, and executive function in new MDMA users. Addiction, 108, 136–145.

Wagner, H. J., Hennig, H., Jabs, W. J., Sickhaus, A., Wessel, K., & Wandinger, K. P. (2000). Altered prevalence and reactivity of anti-

Epstein-Barr virus antibodies in patients with multiple sclerosis. Viral Immunology, 13, 497–502.

Wahl, S., Drong, A., Lehne, B., Loh, M., Scott, W. R., Kunze, S., et al. (2017). Epigenome-wide association study of body mass index, and the adverse outcomes of adiposity. Nature, 541, 81–86.

Wakefield, A. J., Murch, S. H., Anthony, A., Linnell, J., Casson, D. M., Malik, M., et al. (1998). Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet, 351, 637–641.

Walker, E. F., Lewine, R. R. J., & Neumann, C. (1996). Childhood behavioral characteristics and adult brain morphology in schizophrenia. Schizophrenia Research, 22, 93–101.

Walker, F. O. (2007). Huntington's disease. Lancet, 369, 2–26.

Wallace, G. (2018, Aug 9). EPA is ordered to ban the pesticide chlorpyrifos. CNN. Retrieved from https://www.cnn.com/2018/08/09/politics/epa-court-order-ban-pesticide-chlorpyrifos/index.html

Walsh, B. T., & Devlin, M. J. (1998). Eating disorders: Progress and problems. Science, 280, 1387–1390.

Waltes, R., Chiocchetti, A. G., & Freitag, C. M. (2016). The neurobiological basis of human aggression: A review on genetic and epigenetic mechanisms. American Journal of Medical Genetics Part B, 171B, 650–675.

Wan, F.-J., Berton, F., Madamba, S. G., Francesconi, W., & Siggins, G. R. (1996). Low ethanol concentrations enhance GABAergic inhibitory postsynaptic potentials in hippocampal pyramidal

neurons only after block of GABAB receptors. Proceedings of the National Academy of Sciences, 93, 5049–5054.

Wang, A., Costello, S., Cockburn, M., Zhang, X., Bronstein, J., & Ritz, B. (2011). Parkinson's disease risk from ambient exposure to pesticides. European Journal of Epidemiology, 26, 547–555.

Wang, B., Ke, W., Guang, J., Chen, G., Yin, L., Deng, S., et al. (2016). Firing frequency maxima of fast-spiking neurons in human, monkey and mouse neocortex. Frontiers in Cellular Neuroscience, 10, e239.

Wang, B., Zhou, S., Hong, F., Wang, J., Liu, X., Cai, Y., et al. (2012). Association analysis between the tag SNP for sonic hedgehog rs9333613 polymorphism and male sexual orientation. Journal of Andrology, 33, 951–964.

Wang, H. (2018). Modeling neurological diseases with human brain organoids. Frontiers in Synaptic Science. doi:10.3389/fnsyn.2018.00015

Wang, J., Korczykowski, M., Rao, H., Fan, Y., Pluta, J., Gur, R. C., et al. (2007). Gender difference in neural response to psychological stress. Social, Cognitive and Affective Neuroscience, 2, 227–239.

Wang, J. C., Kapoor, M., & Goate, A. M. (2012). The genetics of substance dependence. Annual Review of Genomics and Human Genetics, 13, 241–261.

Wang, R., Chen, C.-C., Hara, E., Rivas, M. V., Roulhac, P. L., Howard, J. T., et al. (2014). Convergent differential regulation of SLIT-ROBO axon guidance genes in the brains of vocal learners. Journal of Comparative Neurology, 523, 892–906.

Wang, S., Tudusciuc, O., Mamelak, A. N., Ross, I. B., Adolphs, R., & Rutishauser, U. (2014). Neurons in the human amygdala selective for perceived emotion. Proceedings of the National Academy of Sciences, E3110–E3119. Retrieved from http://www.pnas.org/content/111/30/E3110.full.pdf

Wang, S., Yu, R., Tyszka, J. M., Zhen, S., Kovach, C., Sun, S., et al. (2017). The human amygdala parametrically encodes the intensity of specific facial emotions and their categorical ambiguity. Nature Communications, 8, 14821. doi:10.1038/ncomms14821

Wang, S.-H., Redondo, R. L., & Morris, R. G. M. (2010). Relevance of synaptic tagging and capture to the persistence of long-term potentiation and everyday spatial memory. Proceedigs of the National Academy of Sciences, 107, 19537–19542.

Wang, S.-M., Lee, C.-U., & Lim, H. K. (2019). Stem cell therapies for Alzheimer's disease: Is it time? Current Opinion in Psychiatry, 32, 105–116.

Ward, B. W., Dahlhamer, J. M., Galinsky, A. M., & Joestl, S. S. (2014). Sexual orientation and health among US adults: National Health Interview Survey, 2013. National Health Statistics Reports, 15, 1–10.

Warren, S., Hämäläinen, H. A., & Gardner, E. P. (1986). Objective classification of motion- and direction-sensitive neurons in primary somatosensory cortex of awake monkeys. Journal of Neurophysiology, 56, 598–622.

Watanabe, T., Kuroda, M., Kuwabara, H., Aoki, Y., Iwashiro, N., Tatsunobu, N., et al. (2015). Clinical and neural effects of six-week administration of oxytocin on core symptoms of autism. Brain, 138, 3400–3412.

Waterland, R. A., & Jirtle, R. L. (2003). Transposable elements: Targets for early nutritional effects on epigenetic gene regulation. Molecular and Cellular Biology, 23, 5293–5300.

Waters, A. J., Jarvis, M. J., & Sutton, S. R. (1998). Nicotine withdrawal and accident rates. Nature, 394, 137.

Watkins, L. R., & Mayer, D. J. (1982). Organization of endogenous opiate and nonopiate pain control systems. Science, 216, 1185–1192.

Watson, C. G., Kucala, T., Tilleskjor, C., & Jacobs, L. (1984). Schizophrenic birth seasonality in relation to the incidence of infectious diseases and temperature extremes. Archives of General Psychiatry, 41, 85–90.

Watson, J. D., & Crick, F. H. C. (1953). Genetical implications of the structure of deoxyribonucleic acid. Nature, 171, 964–967.

Watson, H. J., Yilmaz, Z., Thornton, L. M., Hübel, C., Coleman, J. R. I., Gaspar, H. A., et al. (2019). Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nature Genetics, 51, 1207–1214.

Waxman, S. G., & Ritchie, J. M. (1985). Organization of ion channels in the myelinated nerve fiber. Science, 228, 1502–1507.

Webb, W. B. (1974). Sleep as an adaptive response. Perceptual and Motor Skills, 38, 1023–1027.

Weeks, D., Freeman, C. P., & Kendell, R. E. (1980). ECT: II: Enduring cognitive deficits? British Journal of Psychiatry, 137, 26–37.

Wehr, T. A., Jacobsen, F. M., Sack, D. A., Arendt, J., Tamarkin, L., & Rosenthal, N. E. (1986). Phototherapy of seasonal affective disorder: Time of day and suppression of melatonin are not critical for antidepressant effects. Archives of General Psychiatry, 43, 870–875.

Wehr, T. A., Sack, D. A., & Rosenthal, N. E. (1987). Sleep reduction as a final common pathway in the genesis of mania. American Journal of Psychiatry, 144, 201–204.

Wei, X., & Nielsen, R. (2019). CCR5-Δ32 is deleterious in the homozygous state in humans. Nature Medicine, 25, 909–910. Retrieved from https://www.nature.com/articles/s41591-019-0459-6

Weight loss surgery insurance coverage and costs. (2016, September 20). Obesity Coverage. Retrieved from http://www.obesitycoverage.com/weight-loss-surgery-insurance-coverage-and-costs

Weinberg, R. A. (1989). Intelligence and IQ: Landmark issues and great debates. American Psychologist, 44, 98–104.

Weinberg, R. A., Scarr, S., & Waldman, I. D. (1992). The Minnesota transracial adoption study: A follow-up of IQ test performance at adolescence. Intelligence, 16, 117–135.

Weinberger, D. R., Berman, K. F., Suddath, R., & Torrey, E. F. (1992). Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: A magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. American Journal of Psychiatry, 149, 890–897.

Weinberger, D. R., Berman, K. F., & Zec, R. F. (1986). Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: I.

Regional cerebral blood flow evidence. Archives of General Psychiatry, 43, 114–124.

Weinberger, D. R., & Lipska, B. K. (1995). Cortical maldevelopment, antipsychotic drugs, and schizophrenia: A search for common ground. Schizophrenia Research, 16, 87–110.

Weinberger, D. R., & Wyatt, R. J. (1983). Enlarged cerebral ventricles in schizophrenia. Psychiatric Annals, 13, 412–418.

Weinstein, S. (1968). Intensive and extensive aspects of tactile sensitivity as a function of body part, sex, and laterality. In D. R. Kenshalo (Ed.), The skin senses (pp. 195–222). Springfield, IL: Thomas.

Weir, A. A. S., Chappell, J., & Kacelnik, A. (2002). Shaping of hooks in New Caledonian crows. Science, 297, 981.

Wekerle, H. (1993). Experimental autoimmune encephalomyelitis as a model of immune-mediated CNS disease. Current Opinion in Neurobiology, 3, 779–784.

Welch, B. T., Coelho Prabhu, N., Walkoff, L., & Trenkner, S. W. (2016). Auto-brewery syndrome in the setting of long-standing Crohn's disease: A case report and review of the literature. Journal of Crohn's and Colitis, 10, 1448–1450.

Welch, J. M., Lu, J., Rodriguiz, R. M., Trotta, N. C., Peca, J., Ding, J.-D., et al. (2007). Cortico-striatal synaptic defects and OCD-like behaviours in *Sapap3*-mutant mice. Nature, 448, 894–901.

Weltzin, T. E., Hsu, L. K., Pollice, C., & Kaye, W. H. (1991). Feeding patterns in bulimia nervosa. Biological Psychiatry, 30, 1093–1110.

Wen, W., Zhu, W., He, Y., Kochan, N. A., Reppermund, S., Slavin, M. J., et al. (2011). Discrete neuroanatomical networks are associated with specific cognitive abilities in old age. Journal of Neuroscience, 31, 1204–1212.

Wender, P. H., Rosenthal, D., Kety, S. S., Schulsinger, F., & Welner, J. (1974). Cross-fostering: A research strategy for clarifying the role of genetic and experiential factors in the etiology of schizophrenia. Archives of General Psychiatry, 30, 121–128.

Wender, P. H., Wolf, L. E., & Wasserstein, J. (2001). Adults with ADHD: An overview. Annals of the New York Academy of Sciences, 931, 1–16.

Wennberg, P., Berglund, K., Berggren, U., Balldin, J., & Fahlke, C. (2014). The Cloninger TypeI/TypeII typology: Configurations and personality profiles in socially stable alcohol dependent patients. Advances in Psychiatry, Article ID 346157. doi:10.1155/2014/346157

West, D. B., Fey, D., & Woods, S. C. (1984). Cholecystokinin persistently suppresses meal size but not food intake in free-feeding rats. American Journal of Physiology, 246, R776–R787.

Westerberg, C. E., Florczak, S. M., Weintraub, S., Mesulam, M.-M., Marshall, L., Zee, P. C., & Paller, K. A. (2015). Memory improvement via slow-oscillatory stimulation during sleep in older adults. Neurobiology of Aging, 36, 2577–2586.

Weston, N. M., & Sun, D. (2018). The potential of stem cells in treatment of traumatic brain injury. Curren Neurology and Neuroscience Reports, 18(1). doi:10.1007/s11910-018-0812-z

Wever, E. G. (1949). Theory of hearing. New York, NY: Wiley.

Wever, E. G., & Bray, C. W. (1930). The nature of acoustic response: The relation between sound frequency and frequency of impulses in the auditory nerve. Journal of Experimental Psychology, 13, 373–387.

Wheaton, K. J., Thompson, J. C., Syngeniotis, A., Abbott, D. F., & Puce, A. (2004). Viewing the motion of human body parts activates different regions of premotor, temporal, and parietal cortex. NeuroImage, 22, 277–288.

Wheeler, M. A., Stuss, D. T., & Tulving, E. (1997). Toward a theory of episodic memory: The frontal lobes and autonoetic consciousness. Psychological Bulletin, 121, 331–354.

Wheeler, M. E., Petersen, S. E., & Buckner, R. L. (2000). Memory's echo: Vivid remembering reactivates sensory-specific cortex. Proceedings of the National Academy of Sciences, 97, 11125–11129.

Whipple, B., & Komisaruk, B. R. (1988). Analgesia produced in women by genital self-stimulation. Journal of Sex Research, 24, 130–140.

Whiteside, S. P., Port, J. D., & Abramowitz, J. S. (2004). A meta-analysis of functional neuroimaging in obsessive-compulsive disorder. Psychiatry Research, 132, 69–79.

Whitney, D., Elison, A., Rice, N. J., Arnold, D., Goodale, M., Walsh, V., et al. (2007). Visually guided reaching depends on motion area MT+. Cerebral Cortex, 17, 2644–2649.

Wichmann, T., Bergman, H., & DeLong, M. R. (1994). The primate subthalamic nucleus: III. Changes in motor behavior and neuronal activity in the internal pallidum induced by subthalamic inactivation in the MPTP model of parkinsonism. Journal of Neurophysiology, 72, 521–530.

Wichmann, T., & DeLong, M. R. (2013). The basal ganglia. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), Principles of neural science (5th ed., pp. 982–998). New York, NY: McGraw-Hill.

Wichmann, T., & DeLong, M. R. (2016). Deep brain stimulation for movement disorders of basal ganglia origin: Restoring function or functionality. Neurotherapeutics, 13, 264–283.

Wickelgren, I. (1997). Getting a grasp on working memory. Science, 275, 1580–1582.

Wierenga, C. E., Bischoff-Grethe, A., Melrose, A. J., Irvine, Z., Torres, L., Bailer, U. F., et al. (2014). Hunger does not motivate reward in women remitted from anorexia nervosa. Biological Psychiatry, 77, 642–652.

Wierzynski, C. M., Lubenov, E. V., Gu, M., & Siapas, A. G. (2009). State-dependent spike-timing relationships between hippocampal and prefrontal circuits during sleep. Neuron, 61, 587–596.

Wiesel, T. N., & Hubel, D. H. (1966). Spatial and chromatic interactions in the lateral geniculate body of the rhesus monkey. Journal of Neurophysiology, 29, 1115–1156.

Wilbert-Lampen, U., Leistner, D., Greven, S., Tilmann, P., Sper, S., Völker, C., et al. (2008). Cardiovascular events during world cup soccer. New England Journal of Medicine, 358, 475–483.

Wilcock, G. K., Gauthier, S., Frisoni, G. B., Jia, J., Hardlund, J. H., Moebius, H. J., et al. (2018). Potential of low-dose leuco-methylthioninium bis(hydromethanesulphonate) (LMTM) monotherapy for treatment of mild Alzheimer's disease: Cohort analysis as modified primary outcome in a phase III clinical trial. Journal of Alzheimer's Disease, 61, 435–457.

Wilens, T. E., Faraone, S. V., Biederman, J., & Gunawardene, S. (2003). Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics, 111, 179–185.

Wiles, N., Thomas, L., Abel, A., Ridgway, N., Turner, N., Campbell, J., et al. (2013). Cognitive behavioral therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: Results of the CoBalT randomised controlled trial. Lancet, 381, 375–384.

Wilkinson, M., Wang, R., van der Kouwe, A., & Takahashi, E. (2016). White and gray matter fiber pathways in autism spectrum disorder revealed by ex vivo diffusion MR tractography. Brain and Behavior, 6, e00483. doi:10.1002/brb3.483

Willerman, L., Schultz, R., Rutledge, J. N., & Bigler, E. D. (1991). In vivo brain size and intelligence. Intelligence, 15, 223–228.

Willerman, L., Schultz, R., Rutledge, J. N., & Bigler, E. D. (1994). Brain structure and cognitive function. In C. R. Reynolds (Ed.), Cognitive assessment: A multidisciplinary perspective (pp. 35–55). New York, NY: Plenum Press.

Williams, H., Crane, L. A., Hale, T. K., Esposito, M. A., & Nottebohm, F. (1992). Right-side dominance for song control in the zebra finch. Journal of Neurobiology, 23(8), 1006–1020.

Williams, J. H. G. (2008). Self-other relations in social development and autism: Multiple roles for mirror neurons and other brain bases. Autism Research, 1, 73–90.

Williams, J. H. G., Whiten, A., Suddendorf, T., & Perrett, D. I. (2001). Imitation, mirror neurons and autism. Neuroscience and Biobehavioral Reviews, 25, 287–295.

Williams, K., Brignell, A., Randall, M., Silove, N., & Hazell, P. (2013). Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD) (Review). Cochrane Database of Systematic Reviews, (8), Article CD004677. Retrieved from https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004677.pub3/full

Williams, N. M., Zaharieva, I., Martin, A., Langley, K., Mantripragada, K., Fassdal, R., et al. (2010). Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: A genome-wide analysis. Lancet, 376, 1401–1408.

Williams, R. W., Ryder, K., & Rakic, P. (1987). Emergence of cytoarchitectonic differences between areas 17 and 18 in the developing rhesus monkey. Abstracts of the Society for Neuroscience, 13, 1044.

Williams, T. J., Pepitone, M. E., Christensen, S. E., Cooke, B. M., Huberman, A. D., Breedlove, N. J., et al. (2000). Finger-length ratios and sexual orientation. Nature, 404, 455–456.

Willie, J. T., Chemelli, R. M., Sinton, C. M., & Yanagisawa, M. (2001). To eat or to sleep? Orexin in the regulation of feeding and wakefulness. Annual Review of Neuroscience, 24, 429–458.

Wilson, A. (1998, September 4). Gray matters memory: How much can we remember? And why is it necessary to forget? Orange County Register, p. E1.

Wilson, F. A., Ó Scalaidhe, S. P., & Goldman-Rakic, P. S. (1993). Dissociation of object and spatial processing domains in primate prefrontal cortex. Science, 260, 1955–1958.

Wilson, J. R., Kuehn, R. E., & Beach, F. A. (1963). Modification in sexual behavior of male rats produced by changing stimulus

female. Journal of Comparative and Physiological Psychology, 56, 636–644.

Wilson, M. A., & McNaughton, B. L. (1993). Dynamics of the hippocampal ensemble code for space. Science, 261, 1055–1058.

Wilson, R. I., & Nicoll, R. A. (2001). Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature, 410, 588–592.

Wise, R. A. (2002). Brain reward circuitry: Insights from unsensed incentives. Neuron, 36, 229–240.

Witelson, S. F., Kigar, D. L., & Harvey, T. (1999). The exceptional brain of Albert Einstein. Lancet, 353, 2149–2153.

Witelson, S. F., Kigar, D. L., Scamvougeras, A., Kideckel, D. M., Buck, B., Stanchev, P. L., et al. (2008). Corpus callosum anatomy in right-handed homosexual and heterosexual men. Archives of Sexual Behavior, 37, 857–863.

Witthoft, N., Nguyen, M. L., Golarai, G., LaRocque, K. F., Liberman, A., Smith, M. E., & Grill-Spector, K. (2013). Where is human V4? Predicting the location of hV4 and VO1 from cortical folding. Cerebral Cortex. doi:10.1093/cercor/bht092

Wolff, J. J., Gu, H., Gerig, G., Elison, J. T., Styner, M., Gouttard, S., et al. (2012). Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. American Journal of Psychiatry, 169, 589–600.

Wollberg, Z., & Newman, J. D. (1972). Auditory cortex of squirrel monkey: Response patterns of single cells to species-specific vocalizations. Science, 175, 212–214.

Wolpert, D. M., Pearson, K. G., & Ghez, C. P. J. (2013). The organization and planning of movement. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), Principles of neural science (5th ed., pp. 743–767). New York, NY: McGraw-Hill.

Won, E., & Kim, Y.-K. (2017). An oldie but goodie: Lithium in the treatment of bipolar disorder through neuroprotective and neurotrophic mechanisms. International Journal of Molecular Science, 18, 2679. Retrieved from https://doi.org/10.3390/ijms18122679

Woo, S.-H., Lukacs, V., De Nooij, J. C., Zaytseva, D., Criddle, C. R., Francisco, A., et al. (2015). Piezo2 is the principal mechanotransduction channel for proprioception. Nature Neuroscience, 18, 1756–1762.

Wood, D. L., Sheps, S. G., Elveback, L. R., & Schirger, A. (1984). Cold pressor test as a predictor of hypertension. Hypertension, 6, 301–306.

Woods, B. T. (1998). Is schizophrenia a progressive neurodevelopmental disorder? Toward a unitary pathogenetic mechanism. American Journal of Psychiatry, 155, 1661–1670.

Woods, C. G. (2004). Crossing the midline. Science, 304, 1455–1456.

Woods, S. C. (2004). Gastrointestinal satiety signals: I. An overview of gastrointestinal signals that influence food intake. American Journal of Physiology, 286, G7–G13.

Woods, S. C., & Ramsay, D. S. (2007). Homeostasis: Beyond Curt Richter. Appetite, 49, 388–398.

Woodworth, R. S. (1941). Heredity and environment: A critical survey of recently published material on twins and foster children (A report prepared for the Committee on Social Adjustment). New York, NY: Social Science Research Council.

Wolpert, D. M., Pearson, K. G., & Ghez, C. P. J. (2013). The organization and planning of movement. In E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, & A. J. Hudspeth (Eds.), Principles of neural science (5th ed., pp. 743–767). New York, NY: McGraw-Hill.

Woolf, C. J., & Salter, M. W. (2000). Neuronal plasticity: Increasing the gain in pain. Science, 288, 1765–1768.

Woollett, K., & Maguire, E. A. (2011). Acquiring “the knowledge” of London’s layout drives structural brain changes. Current Biology, 21, 2109–2114.

World Health Organization. (2014). Preventing suicide: A global imperative. Retrieved from https://www.who.int/mental_health/suicide-prevention/world_report_2014/en

World Health Organization. (2019). World report on vision. Retrieved from https://www.who.int/publications-detail/world-report-on-vision

Worley, P. F., Heller, W. A., Snyder, S. H., & Baraban, J. M. (1988). Lithium blocks a phosphoinositide-mediated cholinergic response in hippocampal slices. Science, 239, 1428–1429.

Wray, N. R., & Visscher, P. M. (2010). Narrowing the boundaries of the genetic architecture of schizophrenia. Schizophrenia Bulletin, 36, 14–23.

Wright, J. D., Kennedy-Stephenson, J., Wang, C. Y., McDowell, M. A., & Johnson, C. L. (2004, February 6). Trends in intake of energy and macronutrients—United States, 1971–2000. Morbidity and Mortality Weekly Report, 53(4), 80–82.

Wright, V. L., Georgiou, P., Bailey, A., Heal, D. J., Bailey, C. P., & Wonnacott, S. (2019). Inhibition of alpha7 nicotinic receptors in the ventral hippocampus selectively attenuates reinstatement of morphine-conditioned place preference and associated changes in AMPA receptor binding. Addiction Biology, 24, 590–603.

Wu, C.-S., Jew, C. P., & Lu, H.-C. (2011). Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain: Adverse effect of prenatal exposure to marijuana. Medscape Education. Retrieved from http://www.medscape.org/viewarticle/745279_2

Wu, G., Arbuckle, R., Liu, B., Tao, H. W., & Zhang, L. I. (2008). Lateral sharpening of cortical frequency tuning by approximately balanced inhibition. Neuron, 58, 132–143.

Wu, J. C., & Bunney, W. E. (1990). The biological basis of an antidepressant response to sleep deprivation and relapse: Review and hypothesis. American Journal of Psychiatry, 147, 14–21.

Wurtman, J. J., Wurtman, R. J., Reynolds, S., Tsay, R., & Chew, B. (1987). Fenfluramine suppresses snack intake among carbohydrate cravers but not among noncarbohydrate cravers. International Journal of Eating Disorders, 6, 687–699.

Wyatt, T. D. (2015). The search for human pheromones: The lost decades and the necessity of returning to first principles. Proceedings of the Royal Society, 282, e20142994.

Wynn, K. (1992). Addition and subtraction by human infants. Nature, 358, 749–750.

Wynn, K. (1998). Psychological foundations of number: Numerical competence in human infants. Trends in Cognitive Sciences, 2, 296–303.

Wysocki, C. J., & Preti, G. (2004). Facts, fallacies, fears, and frustrations with human pheromones. Anatomical Record Part A, 281A, 1201–1211.

Xia, X., Yang, Y., Guo, Y., Bai, Y., Dang, Y., Xu, R., & He, J. (2018). Current status of neuromodulatory therapies for disorders of consciousness. Neuroscience Bulletin, 34, 615–625.

Xiao, C., Cho, J. R., Zhou, C., Treweek, J. B., Chan, K., McKinney, S. L., et al. (2016). Cholinergic mesopontine signals govern locomotion and reward through dissociable midbrain pathways. Neuron, 90, 333–347.

Xiao, Z., & Suga, N. (2002). Modulation of cochlear hair cells by the auditory cortex in the mustached bat. Nature Neuroscience, 5, 57–63.

Xie, L., Kang, H., Xu, Q., Chen, M. J., Lia, Y., Thiyagaparajan, M., et al. (2013). Sleep drives metabolite clearance from the adult brain. Science, 342, 373–377.

Xu, H., Cupples, A., Stokes, A, & Liu, C. T. (2018). Association of obesity with mortality over 24 years of weight history. JAMA Network Open, 1(7), e184587. doi:10.1001/jamanetworkopen.2018.4587.

Xu, J., Zhang, J., & Zhang, W. (2018). Antisense RNA: The new favorite in genetic research. Journal of Zhejiang University SCIENCE B, 19, 739–749.

Xu, Y., Padiath, Q. S., Shapiro, R. E., Jones, C. R., Wu, S. C., Saigoh, N., et al. (2005). Functional consequences of a *CKI*d mutation causing familial advanced sleep phase syndrome. Nature, 434, 640–644.

Yacoub, E., Harel, N., & Ugurbil, K. (2008). High-field fMRI unveils orientation columns in humans. Proceedings of the National Academy of Sciences, 105, 10607–10612.

Yam, P. (1998, Winter). Intelligence considered. Scientific American Presents, 6–11.

Yamada, M., Yamada, M., & Higuchi, T. (2005). Remodeling of neuronal circuits as a new hypothesis for drug efficacy. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 29, 999–1009.

Yamanaka, A., Beuckmann, C. T., Willie, J. T., Hara, J., Tsujino, N., Mieda, M., et al. (2003). Hypothalamic orexin neurons regulate arousal according to energy balance in mice. Neuron, 38, 701–713.

Yan, H. (2019, January 21). Superbugs and anti-vaxxers make WHO's list of 10 global health threats. CNN Health. Retrieved from https://www.cnn.com/2019/01/20/health/who-10-threats-to-global-health/index.html

Yanagisawa, T., Fukuma, R., Seymour, B., Hosomi, K., Kishima, H., Shimizu, T., et al. (2016). Induced sensorimotor brain plasticity controls pain in phantom limb patients. Nature Communications, 7, 13209. doi:10.1038/ncomms13209

Yang, C. F., Chiang, M. C., Gray, D. C., Prabhakaran, M., Alvarado, M., Junnti, S. A., et al. (2013). Sexually dimorphic neurons in the ventromedial hypothalamus govern mating in both sexes and aggression in males. Cell, 153, 896–909.

Yang, W., Kelly, T., & He, J. (2007). Genetic epidemiology of obesity. Epidemiologic Review, 29, 49–61.

Yang, Y., Raine, A., Lencz, T., Bihrle, S., LaCasse, L., & Colletti, P. (2005). Volume reduction in prefrontal gray matter in unsuccessful criminal psychopaths. Biological Psychiatry, 57, 1103–1108.

Yang, Y. C., Boen, C., Gerken, K., Li, T., Schorpp, K., & Harris, K. M. (2016). Social relationships and physiological determinants of longevity across the human life span. Proceedings of the National Academies of Science, 113, 578–583.

Yang, Z., & Schank, J. C. (2006). Women do not synchronize their menstrual cycles. Human Nature, 17, 433–447.

Yau, S. Y., Li, A., & So, K. F. (2015). Involvement of adult hippocampal neurogenesis in learning and forgetting. Neural Plasticity, e717958.

Yeni-Komshian, G. H., & Benson, D. A. (1976). Anatomical study of cerebral asymmetry in the temporal lobe of humans, chimpanzees, and rhesus monkeys. Science, 192, 387–389.

Yi, C.-X, la Fleur, S. E., Fliers, E., & Kalsbeek, A. (2010). The role of the autonomic nervous liver innervation in the control of energy metabolism. Biochica et Biophysica Acta, 1802, 416–431.

Yin, Y., Li, Y., & Zhang, W. (2014). The growth hormone secretagogue receptor: Its intracellular signaling and regulation. International Journal of Molecular Sciences, 15, 4837–4855.

Yip, M., Jin, R., Nakajima, H. H., Stankovic, K. M., & Chandrakasan, A. P. (2015). A fully-implantable cochlear implant SoC with piezoelectric middle-ear sensor and arbitrary waveform neural stimulation. IEEE Journal of Solid-State Circuits, 50(1), 214–229.

You, J. S., Hu, S. Y., Chen, B., & Zhang, H. G. (2005). Serotonin transporter and tryptophan hydroxylase gene polymorphisms in Chinese patients with generalized anxiety disorder. Psychiatric Genetics, 15, 7–11.

Youdim, M. B. H., & Riederer, P. (1997, January). Understanding Parkinson's disease. Scientific American, 276, 52–58.

Young, E. (2014, June 3). Brain stimulation: The military's mind-zapping project. BBC Future. Retrieved from http://www.bbc.com/future/story/20140603-brain-zapping-the-future-of-war

Young, L. J., & Wang, Z. (2004). The neurobiology of pair bonding. Nature Neuroscience, 10, 1048–1054.

Young, M. P., & Yamane, S. (1992). Sparse population coding of faces in the inferotemporal cortex. Science, 256, 1327–1331.

Yu, C. J., Du, J. C., Chiou, H. C., Chung, M. Y., Yang, W., Chen, Y. S., et al. (2016). Increased risk of attention-deficit/hyperactivity disorder associated with exposure to organophosphate pesticide in Taiwanese children. Andrology, 4, 695–705.

Yu, M., Linn, K. A., Shinohara, R. T., Oathes, D. J., Cook, P. A., Duprat, R., et al. (2019). Childhood trauma history is linked to abnormal brain connectivity in major depression. Proceedings of the National Academy of Sciences USA, 116, 8582–8590.

Yu, X., Ye, Z., Houston, C. M., Franks, N. P., Brickley, S. G., & Wisden, W. (2015). Wakefulness is governed by GABA and histamine cotransmission. Neuron, 87, 164–178.

Yücel, M., Solowij, N., Respondek, C., Whittle, S., Fornito, A., Pantelis, C., et al. (2008). Regional brain abnormalities associated

with long-term heavy cannabis use. Archives of General Psychiatry, 65, 694–701.

Zada, D., Bronshtein, I., Lerer-Goldshtein, T., Garini, Y., & Appelbaum, L. (2019). Sleep increases chromosome dynamics to enable reduction of accumulating DNA damage in single neurons. Nature Communications, 10(1), 895. doi:10.1038/s41467-019-08806-w

Zaheer, J., Jacob, B., de Oliveira, C., Rudoler, D., Juda, A., & Kurdyak, P. (2018). Service utilization and suicide among people with schizophrenia spectrrum disorders. Schizophrenia Research, 202, 347–353.

Zai, L., Ferrari, C., Dice, C., Subbaiah, S., Havton, L. A., Coppola, G., et al. (2011). Inosine augments the effects of a Nogo receptor blocker and of environmental enrichment to restore skilled forelimb use after stroke. Journal of Neuroscience, 31, 5977–5988.

Zalesky, A., Solowij, N., Yücel, M., Lubman, D. I., Takagi, M., Harding, I. H., et al. (2012). Effect of long-term cannabis use on axonal fibre connectivity. Brain, 135, 2245–2255.

Zandieh, S., Bernt, R., Knoll, P., Wenzel, T., Hittmair, K., Haller, J., et al. (2016). Analysis of the metabolic and structural brain changes in patients with torture-related post-traumatic stress disorder (TR-PTSD) using 18F-FDG PET and MRI. Medicine, 95(15), e3387. doi:10.1097/MD.0000000000003387

Zanos, P., Moaddel, R., Morris, P. J., Georgiou, P., Fischell, J., Elmer, G. I., et al. (2016). NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature, 26, 481–486.

Zebhauser, P. T., Vernet, M., Unterburger, E., & Brem, A.-K. (2019). Visuospatial neglect—A theory-informed overview of current and

emerging strategies and a systematic review on the therapeutic use of non-invasive brain stimulation. Neuropsychology Review, 29, 397–420.

Zeki, S. (1983). Colour coding in the cerebral cortex: The reaction of cells in monkey visual cortex to wavelengths and colours. Journal of Neuroscience, 9, 741–765.

Zeki, S. (1992, September). The visual image in mind and brain. Scientific American, 267, 69–76.

Zepelin, H., & Rechtshaffen, A. (1974). Mammalian sleep, longevity, and energy metabolism. Brain, Behavior and Evolution, 10, 425–470.

Zerbo, O., Qian, Y., Yoshida, C., Grether, J. K., Van de Water, J., & Croen, L. A. (2015). Maternal infection during pregnancy and autism spectrum disorders. Journal of Autism and Developmental Disorders, 45, 4015–4125.

Zhang, F., Vierock, J., Yizhar, O., Fenno, L. E., Tsunoda, S., Kianianmomeni, A., et al. (2011). The microbial opsin family of optogenetic tools. Cell, 147, 1446–1457.

Zhang, H., Huntley, J., Bhome, R., Holmes, B., Cahill, J., Gould, R. L., et al. (2019). Effect of computerised cognitive training on cognitive outcomes in mild cognitive impairment: A systematic review and meta-analysis. British Medical Journal, 9, e027062. Retrieved from https://bmjopen.bmj.com/content/9/8/e027062

Zhang, J., & Webb, D. M. (2003). Evolutionary deterioration of the vomeronasal pheromone transduction pathway in catarrhine primates. Proceedings of the National Academy of Sciences of the United States of America, 100, 8337–8341.

Zhang, J., Zhu, Y., Zhan, G., Fenik, P., Panossian, L., Wang, M. M., et al. (2014). Extended wakefulness: Compromised metabolics in and degeneration of locus ceruleus neurons. Journal of Neuroscience, 34, 4418–4431.

Zhang, L., Benetek, D. M., Fullerton, C. S., Forsten, R. D., Naifeh, J. A., Li, X. X., et al. (2014). PTSD risk is associated with BDNF Val66Met and BDNF overexpression. Molecular Psychiatry, 19, 8–10.

Zhang-James, Y., Fernàndez-Castillo, N., Hess, J. L., Malki, K., Glatt, S. J., Cormand, B., & Faraone, S. V. (2019). An integrated analysis of genes and functional pathways for aggression in human and rodent models. Molecular Psychiatry, 24, 1655–1667.

Zhao, L., Gottesdiener, A. J., Parmar, M., Li, M., Kaminsky, S. M., Chiuchiolo, M. J., et al. (2016). Intracerebral adeno-associated virus gene delivery of apolipoprotein E2 markedly reduces brain amyloid pathology in Alzheimer's disease mouse models. Neurobiology of Aging, 44, 159–172.

Zhou, J. N., Hofman, M. A., Gooren, L. J., & Swaab, D. F. (1995). A sex difference in the human brain and its relation to transsexuality. Nature, 378, 68–70.

Zhou, M., Greenhill, S., Huang, S., Silva, T. K., Sano, Y., Wu, S., et al. (2016). CCR5 is a suppressor for cortical plasticity and hippocampal learning and memory. eLife, 5, e20985. Retrieved from https://elifesciences.org/articles/20985

Zhou, W., Yang, X., Chen, K., Cai, P., He, S., & Jiang, Y. (2014). Chemosensory communication of gender through two human steroids in a sexually dimorphic manner. Cell, 24, 1091–1095.

Zhou, Y., Kierans, A., Kenul, D., Ge, Y., Rath, J., Reaume, J., et al. (2013). Mild traumatic brain injury: Longitudinal regional brain

volume changes. Radiology, 267, 880–890.

Zhou-Hao, L., Yip, P. K., Priestley, J. V., & Michael-Titus, A. T. (2017). A single dose of docosahexaenoic acid increases the functional recovery promoted by rehabilitation after cervical spinal cord injury in the rat. Journal of Neurotrauma. doi:10.1089/neu.2016.4556

Zhu, Q., Song, Y., Hu, S., Li, X., Tian, M., Zhen, Z., et al. (2010). Hereditability of the specific cognitive ability of face perception. Current Biology, 20, 137–142.

Zihl, J., von Cramon, D., & Mai, N. (1983). Selective disturbance of movement vision after bilateral brain damage. Brain, 106, 313–340.

Zillmer, E. A., & Spiers, M. V. (2001). Principles of neuropsychology. Belmont, CA: Wadsworth.

Zimmerman, C. A., Leib, D. E., & Knight, Z. A. (2017). Neural circuits underlying thirst and fluid homeostasis. Nature Reviews Neuroscience. 18, 459–469.

Zimmerman, C. A., Lin, Y.-C., Leib, D. E., Guo, L., Huey, E. L., Daly, G. E., et al. (2016). Thirst neurons anticipate the homeostatic consequences of eating and drinking. Nature, 537, 680–684.

Zion Golumbic, E. M., Ding, N., Bickel, S., Lakatos, P., Schevon, C. A., McKhann, G. M., et al. (2013). Mechanisms underlying selective neuronal tracking of attended speech at a “cocktail party.” Neuron, 77, 980–991.

Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1986). Human amnesia and the medial temporal region: Enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. Neuroscience, 6, 2950–2967.

Zollinger, S. A., & Suthers, R. A. (2004). Motor mechanisms of a vocal mimic: Implications for birdsong production. Proceedings of the Royal Society of London B: Biological Sciences, 271, 483–491.

Zou, K., Deng, W., Li, T., Zhang, B., Jiang, L., Huang, C., et al. (2010). Changes of brain morphometry in first-episode, drug naïve, non-late-life adult patients with major depression: An optimized voxel-based morphometry study. Biological Psychiatry, 67, 186–188.

Zubenko, G. S., Hughes, H. B., Stiffler, J. S., Zubenko, W. N., & Kaplan, B. B. (2002). Genome survey for susceptibility loci for recurrent, early-onset major depression: Results at 10cM resolution. American Journal of Medical Genetics, 114, 413–422.

Zubenko, G. S., Maher, B. S., Hughes, H. B., III, Zubenko, W. N., Stiffler, J. S., & Marazita, M. L. (2004). Genome-wide linkage survey for genetic loci that affect the risk of suicide attempts in families with recurrent, early-onset, major depression. American Journal of Medical Genetics B, 129, 47–54.

Zubin, J., & Spring, B. (1977). Vulnerability: A new view of schizophrenia. Journal of Abnormal Psychology, 86, 103–126.

Zuckerman, M. (1971). Dimensions of sensation seeking. Journal of Consulting and Clinical Psychology, 36, 45–52.

AUTHOR INDEX

aan het Rot, M., 477

Abbott, A., 118

Abbott, D. F., 339

Abe, K., 508

Abel, L., 426

Abelson, J. F., 497

Abi-Dargham, A., 463

Abou-El-Enein, M., 121

Abrahams, B. S., 443

Abrahams, S., 233

Abramov, I., 326

Abramowitz, J. S., 493, 494

Adams, D. B., 205

Adelman, T. L., 99

Ad'es, J., 192

Adler, L. E., 469

Adolphs, R., 246–247

Adriani, M., 281

Adrien, J., 481

Advokat, C. D., 135, 136, 137, 138, 139, 140, 141

Aglioti, S., 532

Agnew-Blais, J. C., 447

Agrawal, A., 153

Agyei, Y., 10, 230

Ahn, J. H., 205

Ahorukomeye, P., 181

Ahuja, C. S., 83

Akbarian, S., 472

Akeju, O., 525

Akheruzzaman, M., 182

Alaerts, K., 443

Alain, C., 280

Albanese, A., 380

Alberini, C. M., 405

Albert, D. J., 262

Albert, M. S., 393

Albertini, R. J., 382

Albrecht, D. G., 335

Albright, T. D., 340

Alexander, C. N., 255

Alexander, G. E., 376

Alexander, J. T., 187

Alexander-Bloch, A. F., 468

Alexandrov, L. B., 140

Aleyasin, H., 261

Alhava, E., 465

Alkire, M. T., 393, 394

Alkon, D. L., 413

Allada, R., 510

Allegretta, M., 382

Allison, T., 506

Almeida, D. M., 78

Alonso, J., 488

Alpert, N. M., 393

Altar, C. A., 480

Altena, E., 518

Altschuler, E. L., 368

Altshuler, L. L., 483, 486

Alvarez, P., 392

Alvord, E. C., 76

Amad, A., 497, 498

Amano, M., 252

Amanzio, M., 364

Amaral, D. G., 390, 391, 392, 414, 422

Amarasingham, A., 43

Ameis, S. H., 448

Ames, M. A., 229

Amin, N. D., 111

Amrollahi, Z., 483

An, Y., 409

Anaclet, C., 517

Anagnostou, E., 442

Anderman, M. L., 173, 174, 176, 177

Anders, T. F., 513

Andersen, R. A., 360

Andersen, S., 366

Anderson, A. K., 242

Anderson, A. W., 341

Anderson, B., 423

Anderson, C. H., 345

Anderson, D. C., 117

Anderson, D. J., 282

Anderson, I. M., 484

Anderson, M., 39

Anderson, N. D., 435

Anderson, P., 411

Anderson, S. W., 242

Ando, J., 429

Ando, K., 99

Andolfatto, P., 11

Andrade, J., 522

Andreani, T. S., 510

Andreano, J. M., 219

Andreasen, N. C., 58, 219, 459, 462, 463

Andrews, G., 218

Andrews, P. J., 518

Andrews-Hanna, J. R., 435

Anglin, M. D., 132

Anguera, J. A., 434

Annarumma, L., 515

Annese, J., 392

Anson, P., 363

Anthony, J. C., 153

Antilla, S. A., 478

Antonucci, N., 445

Aoki, Y., 441, 443

Apkarian, A. V., 366

Appelbaum, L., 515

Arai, Y., 226

Arango, V., 479

Aranow, H., Jr., 381, 382

Araujo, A. B., 205

Arbib, M. A., 305

Arboleda, E., 509

Arbuckle, R., 284

Archer, J., 219, 262

Archer, S. N., 519

Argiolas, A., 207

Arisaka, O., 226

Arman, A. C., 346

Armony, J. L., 305

Armstrong, S. M., 435

Arndt, S., 462

Arnhold, I. J. P., 223

Arnold, M., 527

Arnold, P. D., 494

Arnold, P. E., 488

Arnone, D., 484

Arnott, S. R., 280, 290, 291

Aron, A. P., 243

Aronson, M. D., 187

Arsenault, P., 363

Arzy, S., 361, 532

Asai, M., 183

Åsberg, M., 486

Ascherio, A., 383

Aschoff, J., 508

Ashburn, E., 481

Asher, J. E., 346

Ashok, A. H., 143

Ashour, M. H., 385

Ashtari, M., 143

Askenasy, J. J. M., 514

Aslan, S., 249

Asman, K., 139

Asplund, C. L., 530

Astle, D., 425

Aston-Jones, G., 140

Atkins, H. L., 120

Atkinson, R. M., 467

Augustine, V., 165, 166

Auman, J. I., 301

Aung, Y. K., 476

Avery, R. L., 325

Avidan, G., 341

Avikainen, S., 440

Ax, A., 116, 117, 243

Axelsson, J., 154

Azevedo, F. A. C., 22

Aziz-Zadeh, L., 440, 533

Baaré, W. F. C., 429

Baars, B. J., 525

Babb, S., 139

Bach, A. C., 82

Bach-y-Rita, P., 81

Backes, W. H., 435

Backonja, M.-M., 244

Bahney, J., 22

Bai, D., 443

Baier, B., 532

Bailer, U. F., 193, 194

Bailey, A., 443

Bailey, C. H., 12

Bailey, J. M., 10, 230

Baillet, S., 525

Baizer, J. S., 345

Baker, A. L., 139

Baker, C. I., 110

Baker, C. K., 325

Baker, J. H., 192

Baker, L. A., 264

Bakermans-Kranenburg, M. J., 217

Bakker, J., 216, 221, 222

Balasubramanian, V., 331

Baler, R. D., 188

Baliki, M. N., 366

Balldin, J., 152

Balthazart, J., 216, 280

Bancaud, J., 375

Band, L. C., 207

Bao, A.-M., 221

Baraban, J. M., 483

Barbey, A. K., 429

Barinaga, M., 51, 109

Barker, G. J., 536

Barker, W. B., 431

Barkley, R. A., 447

Barlassina, L., 243

Barlow, D. H., 499

Barnes, C. A., 396, 402

Barnes, C. L., 409

Baro, M., 375

Baron-Cohen, S., 244

Barr, H. M., 136

Barres, B. A., 32

Barres, R., 185

Bartel, P., 513

Bartlett, D. L., 493

Bartlett, E. L., 284

Bartolomei, F., 524

Bartsch, D., 12

Barysheva, M., 486

Basbaum, A. I., 355, 361, 364

Basheer, R., 515

Bassett, M., 115

Bastiaansen, J. A. C. J., 244, 245

Bates, J. F., 373

Bathelt, J., 425

Batista, A. P., 360

Batterham, R. L., 176

Bauer, G., 121

Bauer, L., 154

Bauer, R. M., 342

Baulac, S., 35

Baum, A., 253, 256

Baum, M. J., 211

Bauman, M. J., 84

Baumann, M. H., 139

Baumeister, J.-C., 245

Baumgart, M., 410

Baumgartner, G., 330

Baumgartner, L. S., 286

Baumgartner, N., 228

Baumgartner, T., 442, 443

Bautista, D. M., 355

Baxter, L. R., 7, 484, 485, 493, 494

Bayley, P. J., 391

Beach, F. A., 204

Beal, M. A., 154

Beames, J. R., 261

Beason-Held, L., 409

Beatty, W. W., 233

Bechara, A., 58, 242, 248, 249, 398

Beck, A., 148

Beck, M., 170, 171

Becker, A. E., 192

Becker, B., 141

Beckwith, N., 228

Bedny, M., 76

Beecher, D. K., 258

Beecher, M. D., 304

Begleiter, H., 154

Begley, S., 493

Begré, S., 468

Behrmann, M., 341

Beisteiner, R., 412

Bekar, L., 380

Békésy, G. von, 282, 284

Bekrater-Bodmann, R., 368

Belfort, M. B., 78

Bell, A. P., 229, 230

Beller, E., 446

Bellgowan, P. S. F., 110

Bellinger, D. C., 449

Bellis, D. J., 149

Belliveau, J. W., 339

Bellmann, A., 281

Bellugi, U., 300

Beltagy, A., 524

Beltramo, M., 142

Benca, R. M., 481

Bender, D. B., 340

Benedetti, F., 364

Benedict, C., 183

Bengtsson, C., 179

Benishay, D. S., 230

Benkelfat, C., 494

Bennett, I. J., 425

Bennett, K. M., 376

Bennett, M. V. L., 33

Benoit, E., 28

Benros, M. E., 432

Benson, D. A., 300, 304

Benson, D. F., 414, 533

Benson, M. D., 437

Benton, A. L., 341

Bentz, E.-K., 221

Ben Zion, I. Z., 208

Berenbaum, S. A., 226

Berggren, U., 152

Berglund, A., 223, 224

Berglund, H., 212, 222

Berglund, K., 152

Bergman, H., 380

Berhouma, M., 4

Berk, M., 35

Berke, J., 144

Berkman, N. D., 193

Berlingeri, M., 297

Berlot, R., 435

Berlucchi, G., 532

Berman, M., 262

Berman, M. E., 261

Bermon, S., 204

Bernaerts, S., 443

Bernstein, D. M., 405

Bernstein, I. L., 170

Bernstein, L. J., 527

Berridge, C. W., 36

Berson, D. M., 510

Bertelsen, A., 461

Bertilsson, L., 486

Berton, F., 135

Bervoets, L., 182

Besnard, P., 168

Bessa, J. M., 480

Bessesen, D. H., 186

Bettinger, J. J., 363, 365

Bever, T. G., 303

Beveridge, T. J. R., 138

Bevilacqua, L., 153

Beyer, C., 209

Bhola, R., 105

Bianchi, R., 437

Biddle, N. A., 493

Biederman, J., 446, 447, 448, 449

Biener, A., 179

Bienvenu, O. J., 495

Bigelow, L. B., 470

Biggs, M. M., 481

Bigler, E. D., 55, 425

Billioud, G., 114

Binder, E. B., 490

Binet, S., 420

Bingman, V. P., 80

Bir, C. A., 80

Birbaumer, N., 366, 367, 368

Birklein, F., 367

Birmingham, W., 256

Birney, R. C., 162

Bitsko, R. H., 496

Bittar, R. G., 365

Bitterman, Y., 284

Björkelund, C., 179

Black, M. H., 184

Black, N., 520

Blahak, C., 380

Blake, K. R., 261

Blake, M., 179

Blakeslee, S., 532

Blanchard, D. C., 246

Blanchard, J., 437

Blanchard, R., 232

Blanchard, R. J., 246

Blanke, O., 361, 532

Blehar, M. C., 482

Blihar, D., 536

Blinder, B. J., 193

Bliss, T. V. P., 399

Bloch, D. A., 207

Bloch, G. J., 207

Bloch, V., 514

Bloom, F. E., 133

Bloom, J. S., 297

Bloom, S. R., 188

Bloomer, R. J., 180

Bloomfield, M. A. P., 143

Blum, D., 117

Blum, K., 153

Blumberg, S. J., 496

Bocklandt, S., 232

Bodo, C., 216

Boecker, H., 376

Boets, B., 443

Boeve, B. F., 521

Bogaert, A. F., 229, 232

Bogardus, C., 186

Bogdasarian, R. S., 81

Bohlin, G., 449

Bohman, M., 152

Boillat, M., 262

Boivin, D. B., 509

Boldog, E., 35

Bolger, F., 342

Bolhuis, J. J., 305

Bolles, R. C., 163

Bolwig, T. G., 479

Bonda, E., 360

Bondarenko, E. A., 475

Bonebakker, A. E., 522

Bontempi, B., 395

Bookstein, F. L., 136

Boomsma, D. I., 429

Boone, K., 445

Bor, D., 527

Borenstein, A. R., 78

Boretsky, M., 208

Borge, G. F., 483

Borghuis, B. G., 331

Boring, E. G., 168

Borisovska, M., 41

Born, R. T., 345

Borsook, D., 368

Bortsov, A. V., 365, 366

Bortz, R., 513

Bos, P. A., 263

Bosmans, G., 443

Bosveld, J., 522

Bottini, G., 299

Bouchard, C., 186

Bouchard, M. F., 432, 449

Bouchard, T. J., Jr., 10, 112, 113, 429, 431

Bouchery, E. E., 135

Bouhali, F., 294

Bouhassira, D., 517

Boulenguez, P., 371

Boumans, T., 280

Bourgeois, J.-P., 75

Bourque, C. W., 165

Bouvier, S. E., 341

Bowler, P. J., 244

Bowles, C. A., 253

Bowmaker, J. K., 323, 324

Boycott, B. B., 318

Boynton, G. M., 346

Bozarth, M. A., 138

Braak, E., 407

Braak, H., 407, 527

Bracha, H. S., 470

Bradbury, J., 219

Bradbury, T. N., 470

Bradley, D. C., 343

Bradstreet, J. J., 445

Branch, J., 225

Brand, T., 232

Brandt, J., 380

Brang, D., 346

Brannon, E. M., 427

Brašić, J. R., 442

Bratsberg, B., 430

Braun, A. R., 304

Braun, B. G., 535

Braun, C., 366

Braun, M., 41

Bray, C. W., 281, 282

Bray, G. A., 188

Breasted, J. H., 6

Brecher, E. M., 137, 139, 147, 148

Breedlove, S. M., 226

Breen, G., 475

Breier, J. I., 301

Breitner, J. C., 12

Brem, A.-K., 344

Bremer, J., 204

Bremond-Gignac, D., 296

Brent, D. A., 487

Breslow, J. M., 80

Breton, F., 342

Brewer, J. B., 393

Brewer, R. D., 134, 135

Brickman, A. M., 406

Bridger, E., 402

Brignell, A., 442

Brikell, I., 448

Briley, D. A., 429

Brinkman, C., 375

Britten, K. H., 360

Britten, R. J., 12

Broadfield, D. C., 304

Broberger, C., 173, 174

Broca, P., 6

Bromis, K., 255

Bron, C. R., 402

Bronshtein, I., 515

Brooks, D. J., 413

Brooks-Gunn, J., 530

Brotis, A., 261

Broughton, R., 505, 507, 511, 519

Brown, A. S., 471

Brown, K., 323

Brown, M. T., 363

Brown, R. H., 381

Broyd, S. J., 435

Bruce, C., 340

Brugge, J. F., 282

Brunswick, N., 298

Bruvold, W., 187

Bryant, R. A., 490

Bryden, M. P., 218, 226

Bryk, K., 226

Bryson, S., 381

Bucci, M. P., 296

Buchanan, T. W., 299

Buchanan-Smith, H. M., 305

Buchs, P.-A., 402

Buchsbaum, M. S., 426

Buchwald, H., 188, 189

Buckley, N. A., 465

Buckner, R. L., 294, 394, 395

Buell, S. J., 76

Buffenstein, A., 481

Buhusi, M., 435

Bulik, C. M., 192

Bullmore, E. T., 138, 153–154, 244, 468

Bundlie, S. R., 521

Buneo, C. A., 360

Bunge, S. A., 434

Bunney, B. G., 476

Bunney, W. E., Jr., 472, 475, 481, 483

Buñuel, L., 533

Bunzeck, N., 394

Burgess, A., 79

Burgio, E., 185

Burke, S. M., 221, 222

Burke, S. N., 396

Burkett, J. P., 213

Burnette, C. P., 534

Burt, A., 192

Burt, A. D., 205

Burton, M. P., 345

Burwell, R. A., 192

Buryak, M., 536

Busch, V., 367

Buschkuehl, M., 434

Buschman, T. J., 529

Bushdid, C., 211

Bushnell, I. W., 341

Bushnell, M. C., 260

Butler, P. C., 207

Butters, N., 414

Butterworth, B., 427

Buxhoeveden, D. P., 54, 55

Buxton, O. M., 511

Buysse, D. J., 518

Buzsáki, G., 43

Byrne, R. W., 305

Cabeza, R., 435

Cacioppo, J. T., 180

Caggiula, A. R., 145

Cahalan, M. D., 28

Cahill, L., 218, 219, 393, 398, 404

Calem, M., 255

Cali, J., 428

Calles-Escandón, J., 187

Calvo, N., 299

Campbell, C. M., 258

Campbell, J. N., 362

Campbell, S. S., 507

Camperio Ciani, A., 231

Canale, R. E., 180

Canavan, A. G. M., 377

Cannon, M., 470

Cannon, S. C., 381

Cannon, W. B., 254

Cantalupo, C., 304

Cao, Y. Q., 362

Cao-Lei, L., 258

Capiluppi, C., 231

Carbon, C.-C., 341

Cardno, A. G., 460

Cariani, P. A., 42

Carlisle, M., 256

Carlson, I. H., 364

Carlson, M., 359

Carlson, S. R., 154

Carlsson, H.-E., 119

Carlström, E., 230, 231

Carmichael, M. S., 209

Carmichael, T., 82

Carr, C. E., 289

Carr, K. W., 299

Carr, T. S., 262

Carraher, D. W., 421

Carraher, T. N., 421

Carrera, M. R., 149

Carrier, B., 260

Carroll, J. B., 422

Carroll, M. D., 178

Carter-Saltzman, L., 431

Carvajal, F., 188

Carvalhais, A. B., 506

Casanova, M. F., 54, 55, 467

Cascio, C. J., 534

Caspi, A., 264–265

Cassin, S., 194

Cassone, V. M., 508

Castagnoli, N., Jr., 477

Castellano-Castillo, D., 184

Castellanos, F. X., 449

Castillo, E. M., 301

Castles, A., 296

Castrén, E., 480

Castrén, M., 480

Castro-Caldas, A., 81, 298

Cattaneo, A., 363

Catterall, W. A., 28

Caunca, M. R., 179

Cavanagh, K., 449

Cavanaugh, J., 139

Cawley, J., 179

Caye, A., 447

Ceci, S. J., 421

Cecil, J. E., 176

Cermelli, P., 231

Chafee, M. V., 373

Chai, G., 446

Chakrabarti, B., 244

Chakraborty, S., 339

Chalavi, S., 536

Chamberlain, K., 493

Chan, B. L., 368

Chandler, H. M., 255

Chandrakasan, A. P., 285

Chang, H. S., 398

Chang, M. M., 362

Chang, S., 449

Changeux, J. P., 531

Chanoine, V., 298

Chant, D., 459

Chapman, P. F., 409

Chappell, J., 428

Charbel, F., 301

Charney, D., 488

Chatelle, C., 526

Chatterton, Z., 140

Chau, A., 524, 525

Chaudhari, N., 168

Chau-Wong, M., 463

Chawla, D., 529

Chebli, R., 482

Check, E., 119

Checkley, S. A., 209

Chemelli, R. M., 174

Chen, B., 488

Chen, C., 75

Chen, C. M., 152

Chen, D. F., 80

Chen, F., 120

Chen, F. S., 257

Chen, J. D. Z., 175

Chen, J.-F., 378

Chen, L., 294

Chen, M. C., 484

Chen, N., 105

Chen, X., 168

Chen, Y.-C., 365

Cherian, T., 341

Cherrier, M. M., 436

Cherry, J. A., 211

Cheslow, D., 493

Chew, B., 187

Chi, R. P., 445

Chiang, M.-C., 424, 429

Chiocchetti, A. G., 264

Chirwa, S., 394

Chivers, T., 44

Cho, A. K., 139

Choi, S. H., 407, 408

Choi, S. Y., 442

Chomsky, N., 299

Chong, S. Y. C., 519

Choquet, H., 183

Chou, P., 151

Chou, R., 133

Chou, S. P., 151

Chou, T. C., 174

Chou, Y., 105

Chowdhury, R., 394

Chowdhury, S., 339

Christensen, D. D., 445

Christensen, M. S., 531

Christison, G. W., 467

Christison-Lagay, K. L., 287

Christmann, C., 368

Christoffel, D. J., 104

Christopherson, K. S., 32

Chrousos, G. P., 475

Chu, R., 363, 365

Chuang, R. S.-I., 28

Chung, B. H., 205

Chung, K., 99, 100

Church, T. S., 182

Cicchetti, D. V., 506

Cicchetti, F., 381

Cima, M., 263

Ciompi, L., 486

Cipolotti, L., 533

Cirelli, C., 403, 514, 515

Cirillo, A., 445

Ciryam, P., 408

Clark, L., 147, 249

Clark, V. P., 106

Clarke, R., 300

Clarke, S., 281

Clarkson, A. N., 82

Clarren, S. K., 76

Cleckley, H. M., 535

Cloninger, C. R., 152

Clopath, C., 395

Cloutier, M., 458

Coan, J. A., 244

Coate, D., 507

Coccaro, E. F., 261, 262, 263

Coelho Prabhu, N., 134

Coffman, B. A., 106

Cohen, D. J., 496

Cohen, J. D., 58, 337

Cohen, L., 427

Cohen, L. G., 77

Cohen, M. X., 250

Cohen, N. J., 397

Cohen, P., 188

Cohen, R. M., 449

Cohen, S., 254

Cohen, Y. E., 287

Cohen-Kettenis, P. T., 221, 222, 224

Colapinto, J., 227

Colbourne, L., 485

Colby, C. L., 360, 361

Coldeway, D., 44

Cole, J., 354

Cole, J. H., 536

Cole, S. W., 255, 256

Coleman, D. L., 183, 184

Coleman, P. D., 76

Coleman, R. M., 509

Collaer, M. L., 216, 233

Collman, F., 99

Colman, R. J., 180

Colosio, C., 378

Colt, E. W. D., 364

Comaty, J. E., 135

Compton, W., 151

Considine, R. V., 177

Constantinidis, C., 398

Conway, B. R., 343

Cook, A. S., 217

Cook, T. B., 262

Cooke, D. F., 360

Cooke, S. F., 399

Coon, D., 61, 121, 460, 509

Cooper, H. M., 510

Copp, A., 306

Corbetta, M., 529

Cordier, B., 205

Cordone, S., 515

Corkin, S., 390, 391, 396, 397, 422

Cormand, B., 264

Corna, F., 231

Coronado, V. G., 79

Correll, C. U., 465, 466

Cortés-Cortés, J., 221

Corvol, J.-C., 147

Cosby, A. A., 534

Coscina, D. V., 174

Cosgrove, G. R., 379

Cosmo, C., 106

Costa, E. M. F., 223

Costa, G. de M., 255

Costall, B., 488

Cotzin, M., 290

Coulson, A., 11

Coulston, C. M., 35

Courtet, P., 487

Courtney, S. M., 339

Coury, A., 209

Cox, D. J., 36

Cox, J. J., 365

Coyle, J. T., 135, 473

Craft, S., 436

Craig, A. D., 249, 251

Craig, I. W., 497

Crane, G. E., 476

Crane, L. A., 304

Cribbs, L., 28

Crick, F. H. C., 8, 345, 522, 523

Criss, D., 259

Cristino, L., 178

Cristofori, I., 524

Critchlow, V., 508

Crocker, J., 260

Croft, H. A., 209

Crone, E. A., 434

Crow, T. J., 466

Crowe, R. R., 479

Crutcher, M. D., 376

Cruz-Landeira, A., 378

Cryan, J. F., 78

Cui, L., 207

Culham, J., 338

Culp, R. E., 217

Culverhouse, R. C., 476

Cumella, E. J., 193

Cummings, D. E., 161, 175

Cummings, J. L., 445

Cunniff, C., 470

Cupples, A., 180

Curcio, C. A., 314, 316

Currie, P. J., 174

Curtis, C. M., 188

Curtis, M. A., 81

Cushman, A. J., 103

Cuthbert, B. N., 470

Cyranoski, D., 115, 117, 120

Czeisler, C. A., 509, 519

Czyzewska, M., 528

Dabbs, J. M., Jr., 205, 206, 262, 263

Dacey, D. M., 510

da Cruz, L., 325

Dahl, B. C., 440

Dahlhamer, J. M., 229, 365

Dale, A. M., 294

Dalla Barba, G., 414

Dallenbach, K. M., 290

Dalsager, L., 449

Dalsgaard, S., 446

Dalton, A., 519

Dalton, R., 116

Daly, M., 219

Damasio, A. R., 6, 58, 60, 242, 246–247, 294, 299, 341, 342, 409

Damasio, H., 6, 58, 60, 242, 294, 341

Dammhahn, M., 211

Dan, Y., 334

Dandy, J., 431

Danelli, L., 297

Daneschvar, H. L., 187

Dang-Vu, T. T., 511

Daniel, D., 468

Daniele, A., 380

Daniels, M., 12

Danielson, M. L., 446

Dapretto, M., 440

Darling, R. A., 175

Dartnall, H. J. A., 323, 324

Darwin, C., 4, 9, 12, 299, 303

Das, A., 81

Das, P., 35

Das, R. K., 150

Daschle, T., 120

Daselaar, S. M., 435

Daum, I., 406

Daumann, J., 141

Davatzikos, C., 467

David, A. S., 470

David, D. J., 480

Davidson, J. D., 209

Davidson, J. M., 204, 205

Davidson, M. W., 74

Davidson, R. J., 244, 484

Davies, B., 477

Davies, J. L., 255

Davies, K., 120

Davies, M., 262

Davis, C., 188

Davis, C. M., 169

Davis, J. O., 470

Davis, K. D., 259, 530

Davis, R. L., 404

Davis, S. W., 435

Dawe, S., 139

Dawood, M. Y., 205

Dawson, A. H., 465

Dawson, D. A., 151

Deacedo, B. S., 397

Deacon, T. W., 53, 58

Dealberto, M.-J., 458

de Almeida, R. M. M., 264

Dean, D. C., III, 409

Deary, I. J., 420

DeBauche, B. A., 475

Debruille, B., 342

Decety, J., 260

deCharms, R. C., 363

Deckert, J., 488

De Deyn, P. P., 437

Dediu, D., 306

Deer, B., 116

de Gelder, B., 342

De Gennaro, L., 515

De Geus, E. J., 429

de Gonzalez, A. B., 179

de Graaf, C., 175

de Graaf, T. A., 525

Degreef, G., 473

de Haan, S., 494

Dehaene, S., 296, 426, 427, 445, 525

Deisseroth, K., 99, 104

de Jager, C. A., 435

De Jager, P. L., 410

DeJong, J., 486, 487

de Jonge, F. H., 207

Dekker, A. D., 437

de la Fuente-Fernández, R., 378

Delgado, E., 536

Dell’Amore, C., 428

Della Santina, C. C., 285

DeLong, M. R., 376, 380

DeLuca, G. C., 382

De Luca, V., 470

de Medinaceli, L., 80

Dement, W. C., 513, 514

De Meyer, G., 413

Demicheli, V., 444

Démonet, J. F., 298

Dempster, E., 462

den Hollander, B., 141

Denke, C., 368

Dennis, N. A., 435

Denson, T. F., 261

Denyer, R., 379

Denys, D., 494

Deol, M. S., 279

Depue, R. A., 483

Derntl, B., 218, 488

DeSantis, A. D., 434

de Sauvage, F., 188

Descartes, R., 4, 5, 63, 92

Deschênes, M., 517

De Silva, A., 188

Desimone, R., 340, 343, 345, 398

Desjardins, C., 205

Desmond, J. E., 393

D’Esposito, M., 399

Desrivières, S., 429

Desrosiers, M. F., 413

Dessens, A. B., 226

De Stefano, N., 382

Destrade, C., 395

Deutsch, S. I., 470

De Valois, R. L., 96, 323, 326, 328, 335

Devanand, D. P., 479

Devane, W. A., 142

Devitt, M., 180

de Vivo, L., 515

Devlin, B., 12

Devlin, M. J., 190, 191

Devore, H., 226

DeVry, J., 478

Devue, C., 531

Dew, M. A., 481

de Waal, F. B. M., 530

Deweerdt, S., 442

DeWitt, S. J., 249

Dewsbury, D. A., 204

Dhejne-Helmy, C., 222

Dhond, R. P., 294

Dhurandhar, N. V., 182

Diamond, I. T., 288

Diamond, J., 224

Diamond, M., 220, 226, 227

Diamond, M. C., 423

DiazGranados, N., 483

Dick, D., 153

Dickson, D. A., 258

Diderot, D., 290

Diéguez, C., 173, 174

Diener, H.-C., 377

Diers, M., 368

Dietis, N., 362

Dietrich, T., 435

Dietz, V., 371

DiFiglia, M., 381

Di Lorenzo, P. M., 42, 43

Dilsaver, S. C., 475

Di Martino, A., 441

Di Marzo, V., 178

Dimitrijevic, M. R., 371

Dimond, Y., 441

Dinan, T. G., 435

Dinges, D. F., 513

Di Paolo, T., 378

di Pellegrino, G., 244, 398

di Tomaso, E., 142

Dixen, J., 209

Dkhissi-Benyahya, O., 510

Dobelle, W. H., 323

Dobmeyer, S., 529

Dobson, C. M., 408

Doi, D., 379

Dolan, R. J., 260, 394

Dollfus, S., 462

Dom, G., 148

Dombeck, D. A., 99

Domenice, S., 223

Dominguez, J. M., 207

Donnay, G. F., 299

Dorahy, M., 536

Dörner, G., 216

do Rosario-Campos, M. C., 496

Dostrovsky, J. O., 259, 530

Douaud, G., 435

Doucleff, M., 134

Doughty, C. J., 488

Douglas, M. R., 379

Doust, J., 446

Dowell, D., 133

Dowling, J. E., 318

Downing, P. E., 340

Drachman, D. B., 381

Draijer, N., 536

Dreifus, C., 234

Dresel, S. H., 449

Drevets, W. C., 484, 485

Drgon, T., 306

Drislane, F. W., 296

Driver, J., 345

Drop, S. L. S., 226

Drugan, R. C., 363

Drumi, C., 121

Dryden, S., 187

Dua, T., 436

Dubois, J. M., 28

Duck, S. C., 226

Dudai, Y., 405

Dudley, R., 133

Duffy, J. F., 509

Dufner-Almeida, L. G., 286

Dufour, M. C., 151

Dujardin, K., 514

Duka, T., 134

Dukelow, S., 338

Duncan, G. H., 260

Duncan, J., 423

Dunn, E. C., 476

Dunne, M. P., 10, 230

Dunn-Meynell, A. A., 175

Dupont, P., 344

Durand, J.-B., 319

Durand, V. M., 499

Durso, G. R. O., 260

Dürsteler, M. R., 335

Dutton, D. G., 243

Duzel, E., 395

Düzel, E., 394

Dworak, M., 515

Dwork, A. J., 479

D’Zmura, M., 287

Earle, J. A., 472

Earnest, D. J., 508

Eaton, W. W., 78, 475

Eaves, L. J., 182

Eberhardt, N. L., 186

Ebers, G. C., 382

Ebmeier, K. P., 484

Eccard, J. A., 211

Eddy, K. T., 190

Eden, G. F., 296

Edgerton, V. R., 371

Edlow, B. L., 102

Edwards, R. R., 258

Edwards, T. L., 325

Egger, K., 484

Ehrhardt, A. A., 220, 226, 227

Ehrsson, H. H., 374

Eichenbaum, H., 396, 397

Einarsdottir, E., 365

Eiselt, A.-K., 173, 174

Eisenegger, C., 262

Ekman, P., 244

Eksioglu, Y. Z., 51

Elbert, T., 366

Elger, C. E., 250

Elia, J., 448

Elias, M., 404

Elks, C. E., 183

Ellenbogen, J. M., 511

Ellis, C. E., 377

Ellis, L., 289

Ellis-Davies, G. C. R., 402

Ellison-Wright, I., 468

Elman, J. A., 413

El Marroun, H., 140

Elmore, A. L., 450

Elmquist, J. K., 174

Elsallab, M., 121

Elveback, L. R., 254

Ely, T. D., 398

Enard, W., 12

Endendijk, J. J., 217

Eng, M. Y., 153

Engel, A. K., 527

Engel, S. A., 341

Engel, S. M., 449

Enoch, M.-A., 152

Enomoto, T., 142

Enriori, P. J., 188

Eppig, C., 432

Epstein, R. H., 520

Ercan-Sencicek, A. G., 497

Erhardt, A., 488

Erickson, C. A., 398

Erickson, K. I., 435

Ernfors, P., 480

Ernst, M., 449

Ernulf, K. E., 234

Ersche, K. D., 138, 153–154

Esiri, M. M., 382

Eskandar, E., 379

Eslick, G. D., 410, 444

Esposito, M. A., 304

Ethier, C., 84

Etkin, A., 490

Evans, A., 360

Evans, D. A., 406

Evans, S. M., 446

Evarts, E. V., 369

Evrard, P., 76

Ewald, H., 470

Ezzat, W. H., 436

Fadiga, L., 244

Faedda, G. L., 481

Fahey, J. L., 255

Fahle, M., 406

Fahlke, C., 152

Fahn, S., 378

Faigel, H. C., 36

Falk, D., 423

Falkner, A. L., 261

Fallon, J. H., 393, 394

Falzi, G., 300

Fambrough, D. M., 381

Fan, J., 249–250

Fancher, R. E., 5

Fanelli, D., 116

Fanning, J. R., 261, 263

Fanous, S., 146

Faraone, S. V., 12, 447, 448, 449

Farina, D., 375

Farlow, M., 437

Farmer, A. E., 459

Farooqi, I. S., 183, 188

Farrer, C., 531

Farries, M. A., 379

Farris, H. E., 287

Fasano, A., 380

Fatemi, S. H., 472

Faul, M., 79, 80

Faustman, W. O., 469

Fava, M., 477

Favagehi, M., 253

Fawzy, F. I., 255

Fazio, F., 298

Fehlings, M. G., 83

Fehr, E., 262, 443

Feigenson, G. W., 24

Feinberg, T. E., 531

Feinstein, J. S., 247

Feldman, R., 213

Felleman, D. J., 345

Feng, L., 435

Fenker, D. B., 394

Fenn, K. M., 303

Fenselau, H., 173

Ferguson, S. A., 207

Fergusson, D., 487

Fernandes, C., 420

Fernández, G., 393

Fernández, R., 221

Fernàndez-Castillo, N., 264

Fernández-Real, J. M., 182

Ferrarelli, F., 469

Ferrari, P. F., 305

Ferri, M. J., 182

Ferro, J. M., 297

Ferrucci, L., 255

Fertuck, H. C., 28

Fey, D., 176

Fibiger, H. C., 145

Field, A. E., 179

Fields, H. L., 364

Fiez, J., 65

Filbey, F. M., 249

Filiano, A. J., 257

Finch, C. E., 255

Fincher, C. L., 432

Fink, D. J., 363

Fink, G., 166

Fink, G. R., 191, 531

Finn, E. S., 297

Fiocco, A. J., 252

Fiorino, D. F., 209

Fischbacher, U., 443

Fischer, M., 447

Fischer, T. Z., 366

Fisher, S. E., 306

Fishman, I., 441

Fiske, D. W., 163

Fitzgerald, J. A., 232

Flanagin, V. L., 291

Flanigan, M., 261

Flannery, J. G., 325

Flaum, M., 462

Fleck, M. S., 435

Fleming, R., 256

Fletcher, J. M., 301

Fletcher, K., 447

Fliers, E., 175

Flor, H., 366, 367, 368

Flores, A., 221

Floresco, S. B., 146, 249

Floud, S., 410

Flynn, J. R., 430

Foeli, J., 368

Foerde, K., 191

Fogassi, L., 244, 305

Foland-Ross, L., 486

Folstein, M. E., 12

Foltin, R. W., 208

Ford, J. M., 469

Foreman, M., 221

Fornari, E., 281

Foroni, F., 245

Fosse, M., 399, 514

Fosse, R., 399, 514

Foss-Feig, J. H., 534

Foster, R. G., 509

Fotopoulou, A., 533

Fountas, K. N., 261

Fournier, J. C., 478

Fouts, D. S., 302

Fouts, R. S., 302

Foverskov, E., 420

Fowler, C. D., 80, 153

Fowler, J. S., 146, 477

Fowler, R., 493

Fowles, D. C., 462, 463

Fox, J. W., 73

Fox, M. J., 353, 354, 379, 383

Fox, P., 74

Fox, P. T., 296

Frady, R. L., 262

Fraller, D. B., 412

Francesconi, W., 135

Francis, D. J., 301

Francis, H. W., 285

Frank, G. K. W., 194

Frank, R., 6, 60

Frankish, H. M., 187

Frankland, P. W., 401

Frantz, A. G., 364

Fratiglioni, L., 378

Frayling, T. M., 183

Freed, C. R., 378, 379

Freed, W. J., 80

Freedman, M. S., 509

Freedman, R., 469

Freeman, C. P., 479

Freemantle, N., 423, 467

Freer, R., 408

Freitag, C. M., 264

French, S. J., 176

Freund, P., 82

Frey, J. U., 394

Frey, S., 360

Friberg, U., 232

Friderici, K. H., 449, 450

Fried, I., 45, 284, 340, 341

Fried, P. A., 143

Friederici, A. D., 300

Friedman, J. H., 478

Friedman, J. M., 188

Friedman, N. P., 153

Friedmann, N., 296

Frieling, H., 193

Friend, L., 143

Friesen, W. V., 244

Frings, L., 219

Frischkom, G. T., 435

Frisén, L., 226

Friston, K. J., 109, 249–250, 524, 529

Frith, C. D., 260, 298, 531

Frith, U., 298, 439, 440

Fritsch, G., 5, 6

Fritschy, J.-M., 81

Fritz, H.-C., 140

Frohlich, P. F., 208

Frühbeck, G., 173

Fryar, C. D., 178

Fu, Y.-H., 519

Fudge, J. L., 191

Fujii, M., 294

Fukui, M. M., 529

Fuller, P. M., 516

Fullerton, D. T., 364

Furuichi, T., 305

Furukawa, Y., 142

Fuster, J. M., 58, 398

Gabitto, M., 168

Gabrieli, J. D. E., 393, 397

Gackenbach, J., 522

Gaderman, A. M., 488

Gadian, D. G., 306

Gage, F. H., 80, 121, 402

Gaillard, R., 342, 527

Gainer, H. D., 508

Galaburda, A. M., 6, 60, 296

Galang, J. A., 257

Gale, J. T., 380

Galef, B. G., 170, 171

Galinsky, A. M., 229

Gallese, V., 244, 305, 533

Gallotto, S., 525

Gallup, G., Jr., 530, 531

Gallup, 234

Ganis, G., 339

Ganna, A., 230

Gannon, P. J., 304

Ganzel, B. L., 256

Gao, L., 449

Gao, Q., 174, 175

Garb, J. L., 170

Garcia, J., 169, 170

Garcia-Barrera, M. A., 297

Garcia-Falgueras, A., 221

Garcia-Fernández, J.-M., 509

Gardier, A. M., 480

Gardner, C. O., 475

Gardner, E. L., 146

Gardner, E. P., 355, 359, 360

Gardner, G., 178

Gardner, H., 293

Garelick, T., 205

Garfinkel, L., 518

Garini, Y., 515

Garrigan, P., 326

Garry, M., 405

Gartrell, N. K., 232

Gasparini, F., 378

Gastfriend, D. R., 135

Gatchel, R. J., 253, 256, 258

Gates, G. J., 229

Gatos, H., 261

Gatz, M., 475

Gauthier, I., 341, 342

Gautier, T., 224, 226

Gaviria, M., 301

Gavrilets, S., 232

Gawin, F. H., 138

Gayán, J., 295, 306

Gazdic, M., 120

Gazzaniga, M. S., 63, 534, 535

Gazzola, V., 440, 533

Gearhart, J. P., 227

Gebhard, P. H., 232

Gebhardt, C. A., 414

Geddes, J. R., 423, 467

Gefter, A., 7

Gegenfurtner, K. R., 324

Geiger, A. W., 144

Geiss, L. S., 179

Geist, C. S., 229

Gelfand, M. M., 204, 205

Gelfand, V. I., 74

Gelosa, G., 413

Gendall, K., 193

Geniole, S. N., 262

Genoux, D., 406

Gentner, T. Q., 303

Georgopoulos, A. P., 376

Gerasimenko, Y., 371

Gerloff, C., 105

Gershon, E. S., 475

Gershoni, M., 220

Gertler, P., 434

Geschwind, D. H., 443

Geschwind, N., 57, 292, 293, 300

Getto, C. J., 364

Geyer, M. A., 141

Ghetti, B., 437

Ghez, C. P. J., 372, 376

Ghilardi, J. R., 355

Ghods-sharifi, S., 146

Ghorayshi, A., 228

Ghosh, A., 259

Giaroli, G., 466

Gibbons, J., 261

Gibbons, R. D., 487

Gibbs, R. B., 207

Gibson, J. R., 438

Giedke, H., 481

Giesen, M. E., 536

Gifford, A. M., 287

Gilad, Y., 326

Gilaie-Dolan, S., 249

Gilbert, C. D., 81

Gilbert, J., 440, 441

Gilbertson, M. W., 12, 490, 491

Giles, D. E., 481, 518

Gilissen, C., 437

Gill, K. E., 138

Gilliland, F. D., 140

Gilman, J., 134

Gilman, S. E., 192

Gilmore, J. H., 473

Ginsburg, K., 436

Giovino, G. A., 140

Gipson, C. D., 146

Gisriel, M. M., 256

Gitlin, M. J., 483

Giza, B. K., 169

Gizewski, E. R., 222

Gizowski, C., 165

Gladue, B. A., 233, 262

Glantz, L. A., 473

Gläscher, J., 424

Glaser, R., 253

Glasson, B. I., 377

Glasziou, P., 446

Gleason, R., 482

Glees, P., 81

Glenn, A. L., 266

Glenn, S., 367

Glezer, I. I., 423

Glezer, L. S., 342

Glimcher, P. W., 249

Glover, G. H., 256, 393, 427

Gluecksohn-Waelsch, S., 279

Gmel, G., 136

Goate, A. M., 153, 409, 437

Godfrey, K. M., 184

Goh, S. Y. M., 524

Gold, A. R., 205

Gold, M. S., 137

Gold, P. W., 475, 476, 483

Goldberg, M. E., 42, 357, 360, 361

Goldberg, S. R., 143

Goldey, K. L., 209, 210

Goldin-Meadow, S., 304

Goldman, A., 533

Goldman, D., 153, 262

Goldman, N., 364

Goldman-Rakic, P. S., 339, 373

Goldstein, A. N., 182

Goldstein, E. B., 275, 326

Goldstein, J. M., 218

Goldstein, M. R., 481

Goldstein, R. Z., 137

Gómez, J.-C., 305

Gomez-Mancilla, B., 378

Gomez-Tortosa, E., 301

Gong, Y., 408

Gonzales, K. R., 135

González, G. F., 297

Gonzalez, M., 536

González, R. G., 390, 391, 422

González-Maeso, J., 466

Gooch, C. L., 78

Goodale, M. A., 290, 291

Goodell, E. W., 304

Goodenough, D. R., 512, 513

Goodman, C. S., 71, 74

Goodman, D. C., 81

Goodwin, D. W., 112

Goodwin, F. K., 475, 483

Goodwin, W. E., 223

Gooley, J. J., 509

Gooren, L. J., 221, 222

Gordon, T. P., 117

Gore, J. C., 341

Gorey, C., 28

Gorny, G., 146

Gorski, R. A., 208, 216

Gorwood, P., 192, 497

Gorzalka, B. B., 204, 209, 262

Gotlib, I. H., 484

Gottesman, I. I., 112, 113, 459, 460, 461, 470

Gottesman, L. L., 487

Götz, J., 79, 412

Gougoux, F., 76

Gould, E., 480

Gould, K. G., 117

Gould, S., 144

Gould, T. D., 487

Gouras, P., 326

Gouws, A., 345

Gouzoulis-Mayfrank, E., 141

Govindarajan, A., 401–402

Goy, R. W., 207

Grabowski, T. J., 6, 60, 294

Grace, A. A., 395

Grady, C. L., 280

Grafman, J., 524

Grafton, S. T., 398

Graham, J. M., 205

Graham, K. E., 305

Graham, S., 280

Graham-Kevan, N., 262

Granic, I., 481

Grant, B. F., 151, 497

Grant, J. S., 469

Grant, S., 137, 146, 147

Grau, J. W., 363

Gray, J., 217

Gray, K., 258

Gray, R., 143

Graybiel, A. M., 376, 494

Graziano, M. S. A., 360, 373, 374, 376

Green, E. L., 449

Greenamyre, J. T., 377

Greene, P. E., 378

Greenfeld, L. A., 134

Greenfield, L. J., 207

Greenough, W. T., 76

Greer, M. A., 508

Greer, S. M., 182

Gregory, S. G., 11

Grella, C. E., 132

Grenhoff, J., 140

Gressens, P., 76

Grèzes, J., 305

Griffith, J. D., 139

Griffiths, K. R., 448

Grill, W. M., 380

Grilo, C. M., 180, 182, 183

Grimm, D., 118, 119

Grindlinger, H. M., 495

Groeneveld, M. G., 217

Gross, C. G., 340, 373, 480

Gross, G., 458

Gross, J. J., 263

Grothe, B., 288

Grotzinger, A. D., 262

Grow, R. W., 2

Grubb, M. A., 249

Gruenewald, D. A., 436

Grueter, T., 341

Grupe, D. W., 254

Grüsser, S., 368

Grüter, M., 341

Grüter, T., 341

Grzanna, R., 81

Gu, M., 402

Gu, X., 249–250, 524

Guemez-Gamboa, A., 444

Guerreiro, M., 81, 298

Guerrien, A., 514

Guidotti, A., 472

Guillory, S., 496

Guitart-Masip, M., 394

Gulsuner, S., 462

Gunawardene, S., 447

Güntürkün, O., 530

Gur, R. C., 488

Gurd, J. M., 340

Gurm, H. S., 254

Gurney, A., 188

Gusella, J. F., 11

Gustafson, D., 179

Gustafsson, J.-Å., 216

Gustavson, C. R., 170

Gustavson, D. E., 153

Gustavsson, A., 78

Gutierrez, C. M., 403, 514

Guzowski, J. F., 396

Gwinn, R., 79

Gygax, L., 230

György, B., 286

Haarmeier, T., 339

Haaxma, C., 378

Habel, U., 218

Habib, M., 296, 298

Haedt-Matt, A. A., 193

Haegerich, T. M., 133

Hagelin, J., 119

Hagermann, D., 435

Hagoort, P., 294

Haier, R. J., 393, 394, 426, 427

Haijma, S. V., 467

Halaas, J. L., 183

Hale, L., 509

Hale, T. K., 304

Hales, C. M., 178

Halgren, E., 294

Haliloglu, G., 354

Hall, M. H., 469

Halley, A. C., 208

Hallmayer, J., 521

Hallock, R. M., 43

Halton, K. E., 497

Halweil, B., 178

Hämäläinen, H. A., 359

Hamann, S. B., 398

Hamblin, J., 444

Hamburg, P., 192

Hamer, D. H., 230, 232

Hamilton, J. P., 484

Hamm, A., 300

Hammersmith, S. K., 229

Hamza, T. H., 379

Han, F., 521

Han, L., 354

Han, X., 32

Handelsman, D. J., 204

Haney, M., 208

Hänig, D., 168

Hankins, W. G., 170

Hanlon, C. A., 138

Hanlon, E. M., 80

Hannula-Jouppi, K., 306

Hanse, E., 39

Haqq, C. M., 215

Harada, C. N., 434

Harada, N., 216

Hare, L., 221

Harel, N., 334

Hargrove, M. F., 262

Hari, R., 440

Hariri, A. R., 246, 247

Harley, L. J., 513

Harmon, K. A., 186

Harmon, L. D., 336

Harris, C., 110

Harrison, C. H., 485

Harrison, P. J., 423, 467, 485

Hars, B., 514

Hart, B. L., 204, 207

Hartig, H., 144

Hartline, H. K., 330

Hartman, L., 495

Hartman, T. J., 140

Harvey, A. G., 490

Harvey, S. M., 205

Harvey, T., 423

Hashikawa, K., 261

Hashimoto, M., 78

Hashimoto-Torii, K., 55

Hassabis, D., 396

Hastings, M. H., 511

Hastings, T. G., 377

Hattar, S., 510

Hau, J., 119

Hauglund, N. L., 515

Hauk, O., 294

Haukka, J. K., 458, 476

Hauri, P., 101, 512

Hauser, C. K., 526

Hauser, M. D., 427

Haushofer, J., 262

Hausmann, M., 217

Häusser, M., 28

Hawass, Z., 110

Haworth, C. M. A., 429

Haxby, J. V., 337, 338, 339, 395

Hayes, C., 302

Hayes, K. J., 302

Hayes, R. J., 146

Hazell, P., 442

He, J., 183

He, S., 338

He, Z., 207

Heacock, J. L., 534

Heath, R. G., 245

Hebb, D. O., 399

Hebebrand, J., 193

Hebert, L. E., 406, 411

Hecht, G. S., 42, 43

Hedges, L. V., 218

Hediger, K., 213

Hegde, V., 182

Heil, M., 395

Heim, N., 204

Heinrichs, M., 213, 443

Heipertz, D., 394

Held, J., 139

Heller, A. S., 486

Heller, W. A., 483

Helmholtz, H. von, 5, 6, 282, 286, 320, 321

Helmuth, L., 435

Hen, R., 480

Hendler, R. A., 134

Hendrickson, A. E., 314

Heni, M., 183

Henneberg, M. A., 134

Hennenlotter, A., 244

Hennessey, A., 481

Hennevin, E., 514

Henning, P., 339

Henninghausen, E., 395

Henry, M. E., 479

Hepp-Reymond, M. C., 376

Herbeck, D., 134

Herbert, T. B., 252

Herculano-Houzel, S., 22, 424

Hering, E., 321, 322

Heritch, A. J., 464

Herkenham, M. A., 97

Herman, B. K., 194

Herman, L. M., 304

Hermann, L., 329

Hernán, M. A., 383

Heron, M., 79, 407

Herpertz-Dahlmann, B., 191

Hertz-Picciotto, I., 443

Hervey, G. R., 176, 177

Herzog, D. B., 191, 192

Herzog, H. A., 118

Hesselbrock, V., 154

Heston, L. L., 461, 499, 537

Hettema, J. M., 488

Hevenor, S., 280

Hewitt, J. K., 153

Heywood, C. A., 343

Hichwa, R. D., 294

Hickey, P. T., 105, 378

Hickok, G., 300

Hicks, B. M., 154

Higley, J. D., 263

Higuchi, S., 521

Higuchi, T., 480

Hill, J. O., 181, 186, 187

Hill, N. T., 406

Hill, S. Y., 101, 154

Hill, T., 528

Hillier, L. W., 11

Hind, J. E., 282

Hines, M., 216, 226

Hines, P. J., 211

Hines, T., 423

Hinney, A., 193

Hinson, R. E., 132

Hipolide, D. C., 481

Hirayasu, Y., 466

Hiripi, E., 190

Hirnstein, M., 217, 219

Hirsch, J., 186, 301

Hirsch, L. E., 442

Hirschberg, A., 204

Hitzig, E., 5, 6

Ho, A. C., 325

Hobaiter, C., 305

Hoban, T. M., 482

Hobson, J. A., 399, 514, 515

Hochberg, L. R., 84

Hochner, H., 184

Hockenberry, J., 140

Hoefer, P. F. A., 381, 382

Hof, P. R., 249–250, 524

Hoffman, P. L., 135

Hoffman, V., 132

Hoffmann, K.-P., 339

Hofman, M. A., 221, 222, 233

Hohmann, A. G., 365

Hökfelt, T., 173, 174

Holden, C., 302, 304, 305, 306, 428

Holloway, R. L., 304

Holloway, T., 470, 472

Holmes, C. J., 76

Holowka, S., 299

Holstege, G., 208

Holzer, P., 256

Hömberg, V., 377

Homish, G. G., 140

Hommer, D. W., 134

Honda, S.-I., 216

Honea, R., 466

Hong, C.-J., 487, 488

Hong, S. J., 205

Honkura, N., 402

Hoogman, M., 447

Hooks, B. M., 75

Hoon, M. A., 354

Hope, B. T., 146

Hopkins, R. O., 391

Hopkins, W. D., 303, 304

Hopson, J. S., 211

Horel, J. A., 81

Horgan, J., 15

Horgan, M., 367

Hori, T., 165

Horne, J. A., 506, 513

Horner, P. J., 80

Horton, C., 287

Horton, E. S., 187

Horton, T. J., 186

Horvath, S., 232

Horvath, T. L., 174, 175, 216

Hoshi, E., 373

Hough, C. M., 495, 496

Hough, G. E., 303

Hough, O., 79

Housley, P. C., 217

Houtsmuller, E. J., 232

Howell, M., 521

Howes, O. D., 143, 463

Hser, Y.-I., 132

Hsiao, S. S., 360

Hsiao-ye, Y., 152

Hsu, L. K., 191

Hsueh, B., 99

Hu, N., 230

Hu, S., 230, 231

Hu, S. Y., 488

Hu, V. W., 444

Hu, X. T., 373

Huang, B. S., 82

Huang, Y.-T., 185

Hubbard, E. M., 346

Hubel, D. H., 326, 331, 332, 333, 334, 335, 337, 338

Huber, G., 458, 459

Huber, K. M., 438

Huberman, A. D., 75

Hudson, J. L., 190

Hudspeth, A. J., 279, 288, 306–307, 316, 357

Hugdahl, K., 217

Hughes, H. B., 475

Hull, C. L., 163

Hull, E. M., 207, 209

Hull, J. T., 509

Hulshof, H. J., 481

Hulshoff Pol, H. E., 219

Hulstijn, W., 148

Hummel, K. P., 183

Humphreys, G., 249

Humphries, C., 375

Hunt, G. L., Jr., 232

Hunt, M. W., 232

Hunt, S. M., 244

Hurst, J. A., 306

Hurvich, L. M., 322, 323, 324

Hurwitz, T. D., 521

Husain, M., 434

Hut, R. A., 510

Hutchinson, E. R., 479

Hutchinson, M. R., 149

Hutchison, K. E., 153

Hutchison, W. D., 259, 530

Hutson, P. H., 194

Huttunen, M., 470

Hwang, B. J., 442

Hwangbo, D.-S., 510

Hyde, J. S., 218

Hyman, B. T., 391, 409, 422

Hyman, S. E., 145, 146

Hynd, G. W., 297

Hyvärinen, J., 360

Iacoboni, M., 305, 306, 533

Iacono, D., 413

Iacono, W. G., 154, 192, 483

Ichien, N. T., 249

Idänpään-Heikkilä, J., 465

Iemmola, F., 231

Iervolino, A. C., 221

Ihle, K., 366

Iidaka, T., 441

Iijima, M., 226

Ikram, M. A., 435

Ilies, R., 257

Imperato-McGinley, J., 223, 224, 226

Inda, M. C., 405

Ingvar, M., 364

Innala, S. M., 234

Inokuchi, K., 402

Inouye, S.-I. T., 508

Insel, T. R., 456, 493, 494

Inta, D., 480

Iqbal, K., 437

Irani, B. G., 175

Iriki, A., 359

Irimia, A., 524

Isbister, G. K., 465

Ishihara, K., 479

Ising, C., 412

Itani, O., 518

Itoh, T. Q., 510

Itskov, V., 43

Iurato, S., 357

Ivry, R. B., 377, 534

Iwamura, Y., 359

Iwata, K., 134

Izawa, S., 404

Jacklin, C. N., 217

Jackson, J. C., 275

Jackson, P. L., 260

Jacobs, B. L., 402

Jacobs, G. H., 326

Jacobs, L., 470

Jacobsen, J. H. W., 149

Jacoby, R., 435

Jacquemont, S., 444

Jaeggi, S. M., 434

Jaffard, R., 395

Jaffe, H., 28

Jahanshad, N., 486

Jain, M., 448

Jakubovic, A., 145

Jamal, A., 139

James, B. D., 407

James, D., 143

James, W., 76, 77, 243

Jameson, D., 322, 323, 324

Jandacek, R. J., 78

Jane, J. A., 288

Janiri, D., 484

Janowsky, J. S., 219

Janszky, I., 254

Jardri, R., 497

Jaretzki, A., III, 381

Jarskog, L. F., 473

Jarvis, M. J., 139

Jefferson, T., 444

Jeffords, J. M., 120

Jeffrey, S., 383

Jelicic, M., 263

Jenkins, M. A., 476

Jensen, A. R., 425, 426, 431

Jensen, M. D., 186

Jensh, R. P., 76

Jernigan, T. L., 76

Jervey, J. P., 398

Jessell, T. M., 316, 361

Jew, C. P., 143

Jiang, X., 342

Jiang, Y., 340

Jike, M., 518

Jin, K., 81

Jin, R., 285

Jiradejvong, P., 299

Jirtle, R. L., 185

Joehanes, R., 154

Joestl, S. S., 229

John, E. R., 529

Johnson, A., 396

Johnson, C., 306

Johnson, C. L., 182

Johnson, J. S., 301

Johnson, K. A., 390, 391, 422

Johnson, K. O., 355, 359, 360

Johnson, L. A., 285

Johnson, S. L., 483

Johnson, V., 202–203

Johnsrude, I., 294

Johnston, R. E., 207

Johnstone, T., 109

Jollant, F., 487

Jolles, D. D., 434

Jolles, J., 435

Jonas, J. B., 314

Jones, A. W., 134

Jones, B. C., 204, 206

Jones, D. K., 435

Jones, H. M., 465

Jones, J. G., 371

Jones, K. L., 136

Jones, L. B., 138

Jones, P. B., 470

Jones, P. S., 138, 153–154

Jonides, J., 434

Jons, P. H., 449

Jönsson, B., 78

Jooste, P., 513

Jordan, C. L., 226

Josephs, R. A., 263

Jost, A., 215

Joubert, B. R., 154

Jouvet, M., 517

Jowsey, J. R., 170

Joyce, P. R., 488

Judge, T. A., 257

Julesz, B., 336

Julien, R. M., 135

Julius, D., 355, 361

Jung, R., 345

Jung, R. E., 427

Jung, W. H., 249

Junger, J., 218

Kabir, M. M., 180

Kable, J. W., 249

Kacelnik, A., 428

Kaeberlein, M., 180

Kahn, M. C., 80

Kaiser, J., 115, 121

Kaiwi, J., 232

Kalaska, J. F., 373, 376

Kalina, R. E., 314

Kalinchuk, A. V., 515

Kalivas, P. W., 146

Kalsbeek, A., 175

Kalso, E., 364

Kamali, E., 443

Kanbayashi, T., 521

Kandel, E. R., 12, 28, 36, 75, 118, 316

Kane, J. M., 218, 464

Kaneita, Y., 518

Kanigel, R., 148

Kanny, D., 134

Kanwisher, N., 340

Kao, Y.-H., 331

Kaplan, B. B., 475

Kapoor, M., 153

Kapoula, Z., 296

Kaprio, J., 476

Karahmadi, M., 443

Karimi, P., 443

Karipidis, I. I., 297

Karnath, H.-O., 532

Karni, A., 514

Kasai, H., 402

Kashani, A. H., 120, 325

Kashiwayanagi, M., 167

Kasprian, G., 300

Kastner, S., 529

Katan, M., 432

Katz, S. H., 431

Kaube, H., 260

Kaufman, J., 488

Kausler, D. H., 433

Kawai, N., 427

Kawamura, H., 508

Kawarasaki, A., 360

Kaye, W. H., 191, 193, 194

Kayman, S., 187

Kazim, S. F., 437

Kealey, E. H., 186

Kearney-Ramos, T. E., 150

Keedy, S., 261

Keehn, R. J. J., 441

Keel, P. K., 193

Keele, S. W., 377

Keenan, J. P., 531

Keenan, P. A., 436

Keesey, R. E., 186

Keil, K., 339

Kelleher, R. J., III, 401–402

Keller, A., 211

Keller, K., 427

Kellner, C. H., 479

Kellogg, W. N., 302

Kelly, D. J., 170

Kelly, T., 183

Keltner, N. L., 469

Kemeny, M. E., 255

Kemmotsu, N., 440

Kempton, M. J., 255

Kendell, R. E., 479

Kendler, K. S., 192, 460, 461, 475, 488

Kennaway, D. J., 509

Kennedy, B. K., 180

Kennedy-Stephenson, J., 182

Kennerknecht, I., 341

Kenny, P. J., 153

Kentridge, R. W., 343

Kern, U., 367

Kersken, V., 305

Kessler, R. C., 153, 190, 456, 474–475, 487, 488, 492

Kessler, R. M., 194

Kety, S. S., 459

Keuroghlian, A. S., 228

Keverne, E. B., 211

Keysers, C., 244, 440, 533

Khabbaz, A. N., 99

Khachaturian, Z. S., 407

Khalil, A. A., 477

Khan, N. A., 168

Khan, T. K., 413

Khan-Dawood, F., 205

Khayambashi, S., 249

Kiang, N. Y.-S., 284

Kidd, B. L., 361

Kidd, K. K., 496

Kiecolt-Glaser, J. K., 253

Kieseppä, T., 476

Kigar, D. L., 423

Killin, L. O. J., 410

Kilts, C. D., 398

Kim, E., 442

Kim, J. Y., 461

Kim, K., 43

Kim, K. H. S., 301

Kim, P., 256

Kim, T., 515

Kim, Y.-K., 483

King, B. M., 174

King, C., 464

King, F. A., 117

King, J.-R., 526

King, M.-C., 12

King, R. A., 496

Kinsey, A. C., 232

Kiper, D. C., 324

Kipman, A., 192

Kirk, K. M., 10

Kirkwood, A., 401

Kish, D., 291

Kish, S. J., 141, 142

Kissileff, H. R., 176

Kita, S., 299

Kitamura, T., 395, 402

Klauber, M. R., 518

Klaver, P., 213

Kleber, H. D., 148, 446

Klein, C., 377

Kleinman, J. C., 140

Klenowski, P. M., 147

Kleopoulos, S. P., 207

Klima, E. S., 300

Kline, P., 420

Klink, D. T., 221, 222

Kloner, R. A., 254

Klump, K. L., 192

Knafo, A., 221

Knecht, S., 300

Knierim, J. J., 396

Knight, C. A., 140

Knight, P. L., 279

Knight, R., 78

Knight, Z. A., 165

Knottnerus, G. M., 449

Knowlton, B. J., 376

Koch, C. K., 45, 340

Koch, K., 314

Koch, M., 178

Koch, M. E., 285

Kocher, K. M., 444

Koelling, R. A., 169

Koenig, T., 468

Koeppe, C., 368

Koeppen, B. M., 277

Koester, J., 31

Koester, P., 141

Kogata, T., 441

Kogler, L., 488

Kohl, M., 367

Kohlert, J. G., 207

Kojima, S., 191

Kolb, B., 146

Komada, Y., 520

Komeda, H., 441

Komisaruk, B. R., 208, 209, 364

Kong, L.-C., 189

König, P., 527

Konishi, M., 289

Konkle, T., 76

Koo, K. C., 205

Koob, G. F., 133

Kopelman, M. D., 414

Kordasiewicz, H. B., 381

Korim, W. S., 175

Kornrad, K., 191

Kosambi, D. D., 259

Koscik, T., 219

Kosslyn, S. M., 339

Koubeissi, M. Z., 524

Koulack, D., 513

Koutstaal, W., 394

Kovatchev, B., 36

Koyama, T., 259

Kozlowski, L. T., 140

Kraemer, H. C., 205

Kraepelin, E., 474

Kral, A., 76

Kramarow, E. A., 407

Krank, M. D., 132

Kraskov, A., 45, 341

Kraus, N., 299

Krause, J., 306, 449

Krause, K.-H., 449

Kraut, M. A., 409

Kreiman, G., 340

Kreiter, A. K., 527

Kriegeskorte, N., 110

Kringlen, E., 461

Kripke, D. F., 511, 518

Kritchevsky, M., 414

Kromer, J., 212

Kronauer, R. E., 509

Kroning, J., 508

Krueger, F., 524

Krüger, C., 536

Kruijver, F. P. M., 221

Kubicki, A., 480

Kubischik, M., 339

Kucala, T., 470

Kucher, K., 82

Kuchinad, A., 366

Kudwa, A. E., 216

Kuehn, R. E., 204

Kuehner, C., 475

Kuepper, Y., 263

Kuffler, S. W., 330

Kuhl, P. K., 299

Kuhn, J.-M., 205

Kuja-Halkola, R., 448

Kumar, A., 462

Kumar, D., 410

Kumari, V., 469, 470

Kung, H. F., 449

Kuo, P. X., 209, 210

Kuo, Y.-C., 304

Kupchik, Y. M., 146

Kupfer, D. J., 481

Kurihara, K., 167

Kwak, S. S., 407, 408

Kyrkouli, S. E., 173

La Corte, V., 414

Ladenheim, E. E., 177

Lafee, S., 392

la Fleur, S. E., 175

Lai, C. S. L., 306

Lai, K., 496

Lakonishokl, M., 74

Lally, J., 459

Lalonde, F. M., 395

Lam, P., 488

LaMantia, A. S., 75

Lamb, T., 371

Lambert, J.-C., 409

Lammens, M., 76

LaMotte, S., 134

Lampert, S., 173

Lancaster, E., 535

Lancet, D., 326

Land, G. H., 140

Landau, E., 346

Landry, D. W., 150

Landsness, E. C., 481

Laney, C., 405

Langa, K. M., 410

Lange, C., 462

Lange, C. G., 243

Lange, N., 440

Lange, S., 136

Langer, E. J., 255

Langer, N., 427

Langström, N., 230, 231

Langton, C., 79

Lapis, T. J., 168

Laplane, D., 375

Larkin, K., 207

Larkum, M. E., 54

la Roi, C., 234

Larson, J., 233

Larson, M. E., 408

Larsson, H., 448

Lashley, K., 6

Laska, M., 211

Lassonde, M., 76

Lau, B., 334

Laurent-Demir, C., 395

Laureys, S., 523, 526

Lavie, P., 511

Lawrence, J. M., 184

Lazarini, F., 80

Leask, S. J., 470

Lecendreux, M., 520

Leckman, J. F., 213, 446, 475, 496

Leconte, P., 514

LeDoux, J. E., 242, 400, 405

Lee, B. R., 468

Lee, C.-U., 412

Lee, D. S., 285

Lee, E.-J., 442

Lee, G. P., 242

Lee, J. W., 205

Lee, K.-M., 301

Lee, K.-N., 394

Lee, M., 366

Lee, M.-H., 410

Lee, R., 261, 263

Lee, S., 41, 249

Lee, S. Y., 442

Lee, S.-Y., 147

Lee, T., 463

Leeka, J., 254

Leeman, S. E., 362

Lefaucheur, J.-P., 105

LeFoll, C., 175

Lehky, S. R., 334

Lehrman, S., 119

Leib, D. E., 165

Leibel, R. L., 186

Leibowitz, S. F., 173, 187

Leinenga, G., 79, 412

Leinonen, E. V., 478

Leland, J., 234

Lemon, R. N., 376

Lenane, M. C., 493, 495

Lenneberg, E. H., 299

Lenzenweger, M. F., 460

Leonard, G., 76

Leonard, H. L., 493, 495

Leopold, D. A., 529

Leor, J., 254

LePiane, F. G., 145

Lepore, F., 76

LePort, A. K. R., 404

Lerch, J., 142

Lerer-Goldshtein, T., 515

Lerma-Cabrera, J. M., 188

Lerman, C., 249

Lerner, J. S., 263

Lerner, R. A., 12

le Roux, C. W., 189

Leshner, A. I., 145

Leslie, A. M., 439

Leslie, M., 233

Lesné, S. E., 408

Lester, G. L., 204

LeVay, S., 232, 233, 235

Levenson, R. W., 244

Lévesque, M. F., 379

Levin, B. E., 175

Levin, F. R., 446

Levin, H. S., 76

Levin, N., 188

Levine, J., 166

Levine, J. A., 186

Levinson, S. C., 306

Levitsky, W., 300

Levitt, P., 55, 473

Levy, B., 435

Levy, D. L., 469

Levy, I., 249

Levy, M., 121

Levy, S., 9

Lew, R. A., 507

Lewicki, P., 528

Lewin, R., 82, 438

Lewine, R. R. J., 473

Lewis, D. A., 473

Lewis, D. C., 148

Lewis, H. B., 512

Lewis, J. W., 288

Lewis, M., 530

Lewis, M. B., 244

Lewis, P. D., 76

Lewis, S. W., 472

Lewis, V. G., 226

Lewy, A. J., 482

Li, A., 402

Li, J. Z., 476

Li, S., 518

Li, X., 341

Li, Y., 175

Li, Y. F., 140

Li, Z., 449

Liang, F.-Q., 508

Liang, P., 120

Liao, H.-W., 510

Liberzon, I., 246, 490

Lichtenstein, P., 230, 231

Lichtman, S. W., 185

Lieberman, H. R., 187

Lieberman, J. A., 473

Liechti, M. E., 141

Lightman, S. L., 209

Ligresti, A., 178

Liker, J., 421

Lim, A. S. P., 483

Lim, H. K., 412

Lim, J., 168

Lim, M. M., 212, 213

Limb, C. J., 299

Lin, D., 261

Lin, E., 486

Lin, L., 521

Lindner, A., 339

Lindsay, S., 405

Lindström, P., 212, 222, 232

Linke, A. C., 441

Linnoila, M., 262, 263, 486, 487

Linsenmeier, J. A. W., 230

Linz, M., 458

Liou, Y.-J., 487

Lipska, B. K., 473

Lipton, M. L., 80

Lipworth, L., 383

Lisak, R. P., 381

Lisanby, S. H., 531

Lisberger, S. G., 376–377

Lisman, J. E., 395, 402, 403, 466

Lissner, L., 179

Liszkowski, U., 305

Liu, B., 284

Liu, C. T., 180

Liu, J., 525

Liu, L., 133

Liu, X., 146

Liu, Y., 80

Livingstone, D., 363

Livingstone, M. S., 296, 337, 338, 343

Ljung, R., 254

Lledo, P.-M., 80

Llievski, V., 410

Lobaugh, N. J., 527

Locantore, J. K., 435

Locke, J., 154

Lockhart, D. J., 12

Lockley, S. W., 509

Locurto, C., 431

Loehlin, J. C., 431

Loerwald, K. W., 438

Loewi, O., 33

Loftus, E. F., 405

Logan, B. K., 134

Logothetis, N. K., 109, 110, 337, 529

Logue, M. W., 490

Lomber, S. G., 76

London, E. D., 137

Lönnqvist, J. K., 458, 476

Loos, R. J. F., 183

López, M., 173

Lopez-Gonzalez, M., 299

Lopez-Legarrea, P., 188

López-Rivadulla, L. M., 378

Lopomo, A., 185

Lorrain, D. S., 207, 209

Lott, I. T., 409

Lotze, M., 368

Lou, H. C., 531

Louie, H., 262

Louie, K., 402

Louwerse, A. L., 207

Love, M. C. N., 434

Lowe, K. A., 141, 142

Lowell, B. B., 173, 174, 176, 177

Lowing, P. A., 460, 461

Loy, B., 285

Loyd, D. R., 365

Lozano, A. M., 259, 530

Lu, H.-C., 143

Lu, J., 516

Lu, W., 74

Lubenov, E. V., 402

Luber, B., 531

Lubman, D. I., 139

Lucas, G., 480

Lucas, R. J., 509

Luciano, M., 429

Luczak, S. E., 153

Lukashin, A., 376

Luks, T. L., 496

Luna, B., 341

Lupien, S. J., 255

Lurmann, F., 443

Lüscher, C., 145, 146, 401, 402

Luttrell, A., 260

Ly, D. H., 12

Lynall, R. C., 80

Lyon, L., 519

Lyons, S., 161

Ma, H., 120

Ma, Y.-Y., 147

Maccoby, E. E., 217

MacIsaac, S. E., 82

MacKay, C. E., 466

Mackey, A. P., 434

MacNeilage, P., 427

MacNeilage, P. F., 304

MacNichol, E. F., Jr., 323

Macrae, J. R., 132

Macur, J., 225

Madamba, S. G., 135

Madans, J. H., 140

Madden, D. J., 425

Maddi, S. R., 163

Maddison, D., 253

Madison, D. V., 29

Maechler, P., 392

Maeder, P. P., 281

Maes, H. H. M., 182

Maestu, F., 301

Maffei, M., 188

Magalhães, J. P., 181

Maggi, G., 364

Magistretti, P. J., 39

Magnan, C., 175

Magnasco, M. O., 211

Magnuson, V. L., 230

Magnusson, A., 481

Maguire, E. A., 402, 423

Mah, L., 252, 254

Maheshwari, P., 410

Maheu, M. E., 80

Maho, C., 514

Mahowald, M. W., 521

Mai, N., 343

Maiarù, M., 132

Maier, M. A., 376

Maier, S. F., 363

Mailman, R. B., 465

Mainz, V., 191

Maislin, G., 513

Makrydimas, G., 81

Malach, R., 284

Malarcher, A., 139

Malaspina, D., 466

Malenka, R. C., 104, 145, 146, 401, 402

Malhi, G. D., 35

Malison, R. T., 497

Mallikarjun, A., 287

Malone, S. M., 154

Mamcarz, E., 92

Man, H.-Y., 440, 441

Mancuso, J. J., 104

Mandel, H., 492

Mandemakers, J. J., 234

Maneeton, N., 442

Manes, F., 249

Manfredi, M., 365

Mangels, J. A., 376

Manger, P. R., 31

Mangun, G. R., 534

Mann, J. J., 479, 486, 487

Manning, J. T., 233

Mano, Y., 441

Mansari, M., 517

Mapes, G., 507

Maquet, P., 402, 403

Marchetti, F., 154

Marchione, M., 14

Marcotulli, D., 246

Marczynski, T. J., 488

Marei, H. E., 120

Marentette, P. F., 299

Margoliash, D., 303

Mariani, J., 111

Maric, M. T. T., 249

Marinkovic, K., 294

Marino, L., 530

Marissal, T., 468

Markesbery, W. R., 413

Markowitz, M., 325

Markowitz, S., 507

Marks, D. M., 363

Marks, G. A., 514

Marks, W. B., 323

Marler, M. R., 518

Marler, P., 303

Marois, R., 530

Marotta, R., 442, 444

Mars, M., 175

Marshall, E., 119

Marshall, J., 404

Marshall, J. C., 340

Marshall, K. E., 180

Martens, G., 526

Martin, A., 395

Martin, C., 458

Martin, C. E., 232

Martin, C. K., 181

Martin, D. S., 404

Martin, E. M., 301

Martin, J. B., 381

Martin, K. M., 7, 493

Martin, L. F., 469

Martin, L. L., 244

Martin, M. J., 121

Martin, N. G., 10, 230

Martin, S., 205

Martinez, D., 149

Martini, F., 357

Martinou, J.-C., 80

Martins, I. P., 85, 297, 298

Marucha, P. T., 253

Marx, J., 188, 410

Mascarenhas, M. N., 436

Mascheretti, S., 295

Masica, D. N., 226

Masland, R. H., 317

Masters, W., 202–203

Masterton, B., 288

Mathalon, D. H., 469

Mathers, C. D., 436

Matochik, J. A., 449

Matsui, A., 211

Matsumoto, A. H., 436

Matsumoto, A. M., 436

Matsuzaki, M., 402

Matsuzawa, T., 427

Matt, K. S., 435

Mattay, V. S., 36

Mattingley, J. B., 345

Mattox, J. H., 435

Matud, M. P., 219

Matuszewich, L., 207, 209

Matyi, J. M., 435

Maulik, P. K., 436

May, A., 366

Mayer, D. J., 364

Mayer, E. A., 78

Mayeux, R., 406

Maywood, E. S., 511

Mazmanian, S. K., 78

Mazurek, M. E., 304

Mazzeo, S. E., 192

McAllister, E. J., 182

McCandliss, B. D., 342

McCann, U. D., 141, 142

McCarley, R. W., 469, 515

McCarthy, J., 144

McClearn, G. E., 9

McClelland, J. L., 402

McClintock, M. K., 257

McCluskey, T., 142

McConaha, C., 194

McConnell, R., 443

McCormick, C. M., 233

McCormick, D. A., 377

McCoy, N. L., 205

McCrory, E., 298

McCully, J., 132

McDaniel, M. A., 226

McDonald, J. W., 82, 83

McDonald, K., 303

McDonald, R. J., 397

McDonald, S. A., 254

McDowell, M. A., 182

McEvoy, S. P., 529

McGaugh, J. L., 393, 398, 404, 532

McGeoch, P. D., 361

McGinnis, M. Y., 216

McGorry, P. D., 481

McGough, J. J., 447

McGrath, C. L., 476

McGrath, J., 459, 462

McGue, M., 10, 13, 112, 113, 154, 192, 429

McGuffin, P., 9, 13, 459, 476, 494

McGuire, P. K., 255, 469

McIntosh, A. M., 484

McIntosh, A. R., 435, 527

McIntyre, C. C., 380

McKay, D., 494

McKeefry, D. J., 345

McKeith, I., 378

McKeon, J., 494

McKetin, R., 139

McKinley, M. M., 165

McKinney, S. M., 511

McKinnon, W., 253

McLellan, T. A., 148

McMahon, B., 482

McMahon, F. J., 306

McMenomy, T., 472

McNamara, R. K., 78

McNaughton, B. L., 396, 402

McPhee, J. C., 28

Mechoulam, R., 142

Mecklinger, A., 402

Meerlo, P., 481

Meguerditchian, A., 304

Mehta, M. A., 434

Meier, M. H., 143

Meier, S. M., 488

Meininger, V., 375

Meisel, R. L., 204

Melhem, N., 487

Melis, M. R., 207

Melon, C., 478

Meltzer, H. Y., 477

Meltzoff, A. N., 260

Melzack, R., 260, 364, 366, 532

Mendelson, S. D., 209

Méndez-Alvarez, E., 378

Mendez-David, I., 480

Mendonca, B. B., 223

Meng, M., 341

Meng, Q., 449

Menon, D. K., 366

Menon, V., 427

Meredith, M. A., 76

Merikangas, K. R., 475

Merkel, R. L., 36

Merlin, M. D., 131

Mertz, J. E., 218

Mervis, J., 116

Merzenich, M. M., 279

Mesman, J., 217

Meston, C. M., 208

Mesulam, M.-M., 58

Metzen, D., 430

Metzler-Baddeley, C., 435

Meuli, R. A., 281

Meyer, R. A., 362

Meyer-Bahlburg, H. F. L., 226, 227, 232

Meyerhoefer, C., 179

Meyer-Lindberg, A. S., 468

Meyre, D., 183

Michael-Titus, A. T., 78

Miezin, F. M., 529

Migliore, L., 185

Mignot, E., 521

Mikami, A., 259

Miklowitz, D. J., 483

Mill, J., 462

Millar, J. K., 461

Miller, A., 59

Miller, B. L., 445, 446

Miller, C. J., 297

Miller, D. S., 186

Miller, E. K., 58, 373, 398, 529

Miller, G., 118, 459

Miller, G. A., 470

Miller, J. L., 161

Miller, L. E., 84

Miller, L. S., 482

Miller, M., 234

Miller, N. F., 112

Miller, S. M., 246

Miller, S. R., 297

Milligan, D. N., 170

Mills, R., 181

Milner, B., 298, 300, 390

Milner, D. M., 521

Milner, P., 145, 286

Miltner, W. H. R., 527, 528

Minamoto, F., 226

Mineur, Y. S., 178

Ming, G. L., 80

Minshew, N., 341

Minter, K., 481

Miranda, A., 150

Mirsky, A. F., 460

Mischkowski, D., 260

Mishkin, F., 445

Mishkin, M., 306, 339

Mishra, S. K., 354

Mitchell, D., 513

Mitchell, D. C., 140

Mitchell, D. J., 445

Mitchell, K. S., 192

Mitchell, S. W., 532

Mithoefer, M. C., 141

Mitjans, M., 264

Mitka, M., 188

Mitler, M. M., 506, 507

Mitton, E., 146

Miyake, A., 153

Miyashita, Y., 340, 398

Mizumori, S. J. Y., 396

Mizuno, A., 440

Mizutari, K., 286

Mobbs, C. V., 207

Mody, I., 82

Moffat, S. D., 436

Mogilner, A., 76, 77

Mogilnicka, E., 481

Mohamed, M. A., 442

Mohammed, S., 205, 206

Moir, H. M., 275

Moldin, S. O., 476

Mollon, J. D., 323

Monaco, A. P., 306

Monai, H., 106

Money, J., 220, 226, 227

Monteith, S. J., 79

Montes, D. R., 249

Monti, M. M., 526

Montoya, E. R., 263

Moody, D. B., 304

Mooney, R., 305

Moore, G. J., 436

Moore, T., 376

Moore, V. J., 513

Moore-Ede, M. C., 509, 519

Mora, F., 406

Moran, T. H., 177

Moreno, J. L., 472

Moreno-Jimenez, E. P., 80

Moreno-Küstner, B., 458

Moretto, A., 378

Morey, R. A., 490

Morgan, C., 255

Morgan, D., 428

Morizane, A., 379

Morland, A. B., 345

Mormann, F., 341

Morrel-Samuels, P., 304

Morris, E. K., 405

Morris, J. M., 226

Morris, N. M., 205

Morris, R. B. M., 402, 403

Morris, R. D., 304

Morris, R. G. M., 394

Morrison, S. F., 165

Mors, O., 470

Mortensen, P. B., 446, 470

Morton, J., 439

Moscovitch, M., 341

Moser, D. J., 219

Moser, E. I., 396

Moss, C. F., 290

Moss, H. B., 152

Mottaghy, F. M., 106

Mountcastle, V. B., 359, 360

Mouren-Simeoni, M. C., 192

Mouri, A., 142

Mouritsen, H., 97, 98

Mousavi, S. M., 443

Mpakopoulou, M., 261

Mühleisen, T. W., 476

Muka, D., 154

Mukamel, R., 284

Mulle, J. G., 461

Muller, D., 402

Müller, R.-A., 440

Muller, R. U., 403, 441

Müller, U., 279

Müller-Bergh, J. A., 314

Mullington, J. M., 513

Munafò, M. R., 484

Munch, K., 302

Muñoz, M., 509

Munzar, P., 143

Muotri, A., 121

Muraro, P. A., 383

Muravieva, E. V., 405

Murphy, A. Z., 365

Murphy, D. L., 483, 494

Murphy, E. A., 12

Murphy, G., 4

Murphy, G. M., Jr., 423

Murphy, M. R., 209

Murray, J. I., 11

Murray, R. M., 469, 470, 472

Murrell, J., 437

Murrough, J. W., 477

Murthy, V., 465

Muschamp, J. W., 209

Must, A., 179

Mustafa, S., 149

Mustanski, B. S., 230, 231

Mutz, J., 479

Muzio, J. N., 514

Myers, J. M., 488

Nabeshima, T., 142

Naccache, L., 525

Nachev, P., 249

Nader, K., 405

Naeser, M. A., 414

Naglieri, J. A., 431

Nair, A., 441

Nairne, J. S., 203, 421

Nakajima, H. H., 285

Nakashima, T., 165

Naliboff, B. D., 219, 255

Nanda, P., 468

Napollelo, E. M., 296

Narr, K. L., 261, 424

Narvaes, R., 264

Nash, J. M., 523

Natarajan, N., 450

Naumann, G. O. H., 314

Naylor, R. J., 488

Neale, M. C., 10, 182, 230, 460, 475, 488

Nebes, R. D., 63

Nedergaard, M., 515

Neisser, U., 420, 431

Nelken, I., 284

Nelson, C., 188

Nelson, D. A., 303

Nelson, L., 29

Nelson, R. J., 263

Nestler, E. J., 145, 146, 462

Nestor, P. G., 469

Nettelbeck, T., 431

Netter, F. H., 215

Neuman, T., 379

Neumann, C., 473

Neumann, D. L., 218

Neville, H. J., 300

New, M. I., 225

Newbury, D. F., 306

Newell, D. W., 79

Newen, A., 243

Newman, A. L., 232

Newman, E. A., 39

Newman, J. D., 279

Newman, R. I., 255

Newman, R. S., 287

Newport, E. L., 301

Newport, F., 229

Ng, S. W., 182

Ngun, T. C., 231

Nguyen, H. B., 218, 222

Nichelli, P., 299

Nichols, R. C., 431

Nicklas, J. A., 382

Nicoll, R. A., 29, 142–143

Nield, D., 115

Nielsen, A. S., 470

Nielsen, H. S., 446

Nielsen, J. B., 531

Nielsen, R., 120

Niemeier, A., 366

Nieto, F. R., 28

Nigg, J. T., 449, 450

Niimura, Y., 211

Nijenhuis, E. R. S., 536

Nijhuis, F. A. P., 435

Nikolas, M. A., 449, 450

Nikonenko, I., 402

Nimkarn, S., 225

Niparko, J. K., 285

Nisbet, R., 79

Nisbett, R. E., 431

Nishitani, N., 440

Nitschke, J. B., 484

Niznikiewicz, M. A., 469

Noakes, T. D., 165

Noar, S. M., 434

Nobili, L., 521

Noble, K. G., 342

Nobre, K., 425

Noda, Y., 142

Nongpiur, A., 496

Nopoulos, P., 219

Nori, S., 83

Norman, B. F., 226

Normile, D., 14

Norton, S., 76

Nottebohm, F., 304

Nour, M. N., 463

Novati, A., 481

Nowell, A., 218

Nowicki, S., 305

Nulman, I., 138

Nunez, A. A., 508

Nunn, J. A., 346

Nurmikko, T., 367

Nurnberger, J., 481

Nusbaum, H. C., 303

Nussbaum, R. L., 377

Oakson, G., 517

Oates, J. A., 139

Oberman, L. M., 245, 440

O’Brien, C., 401

O’Brien, C. P., 148

O’Brien, N. L., 466

Oby, E. R., 84

O’Callaghan, E., 470

Ocklenburg, S., 297

O’Connor, D. H., 529

O’Connor, J., 144

O’Connor, S., 154

O’Dean, S. M., 261

O’Dell, T. J., 75

O’Doherty, S. B., 260

Ogden, C. L., 178

Ogden, J., 81

Ohno, M., 401

Okanoya, K., 305

O’Keane, V., 435

Okubo, Y., 464

Okun, M. S., 497

Olanow, C. W., 377, 378

Olazábal, D. E., 213

Oldenburger, W. P., 207

Olds, J., 145

Olds, R. J., 488

O’Leary, D., 219

Olek, M. J., 383

Olender, T., 211

Olesen, J., 78

Oliet, S. H. R., 39

Olincy, A., 469

Oliviera, B. M., 29

Olkinuora, M., 465

O'Loughlin, P., 205

Olsen, C. M., 147

Olshansky, S. J., 180

Olson, E. J., 521

Olson, H. C., 136

Olson, R. K., 295

Olulade, O. A., 296

O'Neal, J. H., 465

Ong, K. K., 183

Ono, Y., 429

Onstad, S., 461

Oo, K. Z., 476

Ooms, M. P., 207

O'Rahilly, S., 188

Orban, G. A., 340, 344

O'Reilly, K. B., 133

O'Reilly, R. C., 402

Orff, H., 518

Orgogozo, J. M., 375

Orlans, F. B., 118

Orlovska, S., 470

O’Rourke, D., 482

Ortigue, S., 361

Ortiz-Catalan, M., 77, 368

Orwoll, E. S., 219

O’Shaughnessy, D. M., 360

Østergaard, S. D., 446

Ostry, D., 299

O’Sullivan, M. J., 435

Osvath, M., 428

Otten, L. J., 527

Oulhaj, A., 435

Ounsley, J., 305

Oviatt, S. K., 219

Oviedo-Joekes, E., 149

Owen, A. M., 526

Owen, M. J., 9

Owens, N., 481

Ozbay, F., 256

Özyürek, A., 299

Pääbo, S., 326

Padhee, B., 255

Padhy, S. K., 255

Pakstis, A. J., 431

Palfi, S., 379

Palmer, A. R., 283

Palva, I. P., 465

Panda, S., 510

Pandarinath, C., 84

Pandey, M., 354

Paolicelli, R. C., 410

Papa, G., 245

Papalambros, N. A., 515

Pappone, P. A., 28

Paquin, S., 264

Paré, D., 517

Parent, J. M., 81

Park, A., 523

Park, B., 363

Park, M., 205, 444

Parker, E. S., 404

Parker, S. E., 437

Parsonage, S., 186

Partonen, T., 476

Paşca, S. P., 111

Pascual-Leone, A., 76

Pashler, H., 110

Passamonti, L., 263

Passilly-Degrace, P., 168

Passingham, D., 466

Passingham, R. E., 305, 374

Pastalkova, E., 43

Pastor, L., 458

Patel, A. B., 438

Patel, A. J., 29

Patel, V., 515

Paterakis, K. N., 261

Paterson, R. W., 413

Pattatucci, A. M. L., 230

Paule, M. G., 207

Paulesu, E., 297, 298

Pauls, D. L., 496

Paulus, M., 191

Pavăl, D., 442

Pavan, C., 515

Pavlopoulos, E., 406

Pearlman, A., 120

Pearlson, G. D., 470

Pearson, K. G., 372, 376

Pecka, M., 288

Pedersen, M. G., 446

Pedersen, N. L., 475

Pedersen, N. P., 516

Pedersen, N. W., 521

Peeters, R., 428

Pell, A. N., 168

Pellegrino, A. S., 103

Pellegrino, L. J., 103

Pelphrey, K., 76

Peñas-Lledó, E., 192

Penfield, W., 58, 61, 62, 359, 372, 395

Penfold, B., 443

Peng, Y., 168

Penke, L., 424, 425

Pennacchio, L. A., 11

Penner, M. H., 168

Pentel, P. R., 149

Pepperberg, I. M., 303

Percy, Z., 221

Pereira, E., 168

Pereira, R., 460

Perez-Reyes, E., 28

Perkel, D. J., 379

Perkins, A., 232

Perlis, M. L., 518

Perrett, D. I., 534

Perrin, J. S., 76, 486

Perron, M., 76

Perrone, P., 300

Persson, J., 219

Pert, C. B., 96, 97, 132

Peterhans, E., 330, 335

Peters, J. C., 181

Peters, J. M., 140

Peters, S., 305

Petersen, M. R., 304

Petersen, S. E., 296, 395, 529

Peterson, B. S., 484, 530

Peterson, J. B., 134, 263

Peterson, M. J., 481

Peterson, R. E., 223, 224, 226

Petersson, K. M., 364

Petit, D., 520

Petitto, L. A., 299, 300, 303

Petrides, M., 360

Petrovic, P., 364, 365

Petrulis, A., 207

Petukhova, M., 474–475

Peuskens, H., 344

Pfaff, D. W., 166, 207

Pfaus, J. G., 207

Pfrieger, F. W., 32

Phan, K. L., 246, 261, 263

Phelps, E. A., 242

Phelps, J. A., 470

Phelps, M. E., 7, 493

Phillips, A. G., 145, 209

Phillips, R. J., 175, 176

Picard, F., 524

Picard, J. J., 76

Picciotto, M. R., 178

Pichardo, M., 226

Pickar, D., 465

Pickavance, L., 187

Pickens, C. L., 146

Pickering, R. P., 151

Pidsley, R., 462

Pierau, F. K., 165

Pierre, M. B., Jr., 140

Piet, R., 39

Pietiläinen, K. H., 182

Pietrokovski, S., 220

Pietschnig, J., 424, 425

Pigarev, I. N., 529

Pihl, R. O., 134, 263

Pike, G. B., 76

Pillard, R. C., 10, 230

Pillay, P., 31

Pilowsky, L. S., 464, 465

Pinel, P., 426–427, 460

Pineros, V., 257

Pinker, S., 299, 306, 426

Pinsk, M. A., 529

Pinter, M. M., 371

Pinus, U., 36

Pinyon, J. L., 286

Piomelli, D., 142

Pi-Sunyer, X., 176, 186

Pitiot, A., 76

Pizzagalli, D., 484

Plank, M., 181

Platje, E., 263

Platts-Mills, T. F., 365

Plomin, R., 9, 12, 13, 221, 429, 430

Plotnik, J. M., 530

Poggio, G. F., 338

Poggio, T., 338

Pogue-Geile, M. F., 180, 182, 183

Poirer, C., 280

Polderman, T. J. C., 221

Pollice, C., 191

Pollo, A., 364

Pomeroy, W. B., 232

Poole, W. K., 254

Pope, H. G., Jr., 190

Popkin, B. M., 182

Popova, S., 136

Poranen, A., 360

Porjesz, B., 154

Porrino, L. J., 138

Port, J. D., 493

Porter, J., 211

Porto, P. R., 493

Posthuma, D., 429

Postle, B. R., 399

Postma, P., 469, 470

Potenza, M. N., 194

Potter, W. Z., 479

Poulain, D. A., 39

Pournaras, D. J., 189

Povinelli, D. J., 530, 531

Powell, T. P. S., 359, 360

Power, R. A., 462

Powers, J., 225

Powley, T. L., 175, 176, 186

Prabhakar, S., 11

Pracht, E., 78

Prather, J. F., 305

Prehn-Kristensen, A., 106

Prendergast, B. J., 257

Prescott, C. A., 488

Press, G. A., 414

Preston, J. D., 465

Preston, S. H., 180

Preti, G., 211

Pretorius, A., 462

Price, D., 444

Price, D. D., 259, 260

Price, J., 475

Price, R. A., 496

Priestley, J. V., 78

Prince, M., 470

Pringsheim, T., 442

Prior, H., 530

Proal, E., 448

Probst, C., 136

Prufer, K., 302

Prusiner, S. B., xv

Pryor, T. L., 194

Przeworski, M., 326

Ptáček, L. J., 519

Puce, A., 339

Pueschel, E. B., 441

Pulvermüller, F., 294

Purves, D., 279

Putnam, K., 484

Puts, D. A., 208, 226

Pyter, L. M., 257

Qadri, Y. J., 366

Qin, B., 435

Qin, Y.-L., 402

Qiu, X., 510

Qu, Y., 249

Quian Quiroga, R., 45, 341

Quirk, G. J., 403

Rabl, U., 257

Raboch, J., 205

Ragozzino, M. E., 58

Ragsdale, D. S., 28

Rahman, Q., 230, 231, 233

Raible, F., 509

Raichle, M. E., 296, 484

Raine, A., 261, 266

Raine, R., 266

Rainer, G. S., 373, 398

Rainville, P., 260

Raja, S. N., 362

Rajah, M. N., 527

Rajendran, L., 410

Rakic, P., 55, 75, 93

Ramachandran, V. S., 245, 346, 368, 440, 532

Ramchandani, V. A., 134

Ramey, C. T., 431

Ramón y Cajal, S., 33, 82, 83, 95

Ramoz, N., 497

Ramsay, D. S., 174

Ramsay, E., 495

Ramus, F., 296

Randall, M., 442

Rankin, S. K., 299

Rao, A. N., 74

Rao, S. C., 373, 398

Rapoport, J. L., 492, 493, 495

Rasmussen, T., 58, 298, 359, 372

Ratcliff, M., 508

Ratliff, C. P., 331

Ratliff, F., 330

Rattinger, G. B., 435

Rauch, S. L., 393, 494

Rauch, V., 432

Rauschecker, J. P., 280

Ravelli, G. P., 185

Raven, J. C., 421

Ray, L. A., 153

Ray, R. A., 152

Ray, W. J., 462

Read, J. D., 405

Read, S. L., 445

Reber, P., 2

Rebert, C. S., 255

Recht, L. D., 507

Rechtshaffen, A., 506

Reddihough, D., 442

Reddy, A. B., 511

Redelmeier, D. A., 529

Redinbaugh, M. J., 523

Redish, A. D., 396

Redondo, R. L., 394

Reed, G. W., 181

Reed, J. J., 392

Reed, T. E., 425, 426

Rees, G., 529

Refsum, H., 435

Regalado, A., 120

Rehm, J., 456

Reich, T., 476

Reichenberg, A., 473

Reichmann, F., 257

Reilly, D., 218

Reiman, E. M., 435

Reimers, S., 233

Reinders, A. A. T. S., 536

Reiner, W. G., 227

Reininghaus, U., 191

Reinisch, J. M., 226

Reisberg, B., 411

Reisner, S. L., 228

Reiss, A. L., 427

Reiss, D., 530

Relkin, N. R., 301

Rempel-Clower, N. L., 392

Ren, X., 213

Renault, B., 342

Renier, L. A., 76

Renshon, J., 263

Renthal, W., 462

Requin, J., 376

Resko, J. A., 207

Resnick, S. M., 409

Rettew, D. C., 495

Reynolds, C. P., 253

Reynolds, S., 187

Rezaii, N., 459

Rezak, M., 379

Riad, J. K., 262

Ribary, U., 525

Ribiez, S. R., 484

Ricart, W., 182

Ricaurte, G. A., 141, 142

Rice, F., 112, 140

Rice, J. P., 476

Rice, M. L., 306

Rice, W. R., 232

Richardson, C., 367

Richter, M. A., 488, 494

Ridaura, V. K., 182

Riedel, G., 393

Riederer, J., 194

Riederer, P., 377

Rieger, G., 230

Riehle, A., 376

Riesenhuber, M., 342

Rietveld, E., 494

Rieux, C., 510

Rijlaarsdam, J., 449

Rijo-Ferreira, F., 510, 511

Riley, K. P., 413

Rimmele, U., 213

Ringkamp, M., 362

Riolo, J. V., 209

Risoud, M., 288

Rissman, E. F., 216

Ritchie, J. M., 31

Ritterband-Rosenbaum, A., 531

Rivera, S. M., 427

Rivetti, A., 444

Rizvi, S. W., 221

Rizzolatti, G., 244, 305, 373, 376

Robbins, T. W., 138, 147, 154, 249

Roberts, A. I., 305

Roberts, S. G. B., 305

Robertson, L. C., 527

Robertson, M., 520

Robinette, C. D., 461

Robinson, P., 494

Robinson, T. E., 146

Rocha-Miranda, C. E., 340

Rockland, M., 367

Rodin, J., 181

Rodriguez, A., 449

Rodriguez, I., 211

Rodriguez-Raecke, R., 366

Roe, A. W., 338

Roeber, J., 134

Roecklein, K. A., 510

Roeder, K., 12

Roenneberg, T., 509, 519

Roffwarg, H. P., 481, 513, 514

Rogan, M. T., 400

Rogart, R. B., 31

Rogeberg, O., 430

Roland, P. S., 285

Rolls, B. J., 169, 171, 186

Rolls, E. T., 169

Rombouts, S. A. R. B., 434

Ronning, M. E., 431

Roorda, A., 324

Roozendaal, B., 398

Roper, S. D., 168

Rose, J. E., 282

Rose, R. J., 13

Roselli, C. E., 207

Rosen, G. D., 296

Rosen, L. N., 481

Rosen, S., 182

Rosenbaum, M., 186

Rosenberg, C. R., 44

Rosenberg, E., 143

Rosenberg, H., 42

Rosenstand, A., 531

Rosenthal, D., 459

Rosenthal, N. E., 481, 482

Rösler, A., 205

Rösler, F., 395

Ross, G. W., 378

Rossini, P. M., 515

Roth, G. L., 279

Roth, W. T., 469

Rothe, C., 488

Rothman, J. M., 168

Rots, M. G., 437

Rouw, R., 346

Rowe, E. A., 169, 171

Rowe, J., 303

Rowe, M. L., 304

Rowland, L. P., 381, 382

Roy, A., 486, 487

Roy, R. R., 371

Rozin, P., 167, 170, 171

Ruan, W. J., 151

Rubens, A. B., 300

Rubenstein, B. S., 514

Rubert, E., 303

Rubino, F., 189

Rudorfer, M. V., 479

Ruether, W., 366

Rugg, M. D., 526

Rush, A. J., 481

Rushton, J. P., 431

Rushton, W. A. H., 30

Rusiniak, K. W., 170

Russ, T. C., 410

Russell, S., 325

Russo, S. J., 261

Rutherford, W., 281

Rutledge, J. N., 55, 425

Rutter, M., 438, 439

Rutz, C., 428

Ryan, D. B., 526

Ryan, M. J., 287

Ryba, N. J. P., 168

Ryder, K., 75

Rylaarsdam, L., 444

Rzhetsky, A., 443

Saalmann, Y. B., 529

Saarimäki, H., 246

Sabbe, B., 148

Sabesan, R., 324

Sabetghadam, A., 175

Sacco, K. A., 469

Sachs, B., 204

Sack, A. T., 105, 525

Sack, D. A., 481

Sack, R. L., 482

Sackeim, H. A., 479, 484

Sacks, D. A., 184

Sacks, J. J., 135

Sacks, O., 61, 314, 340, 341, 354, 356, 445, 446, 496, 532, 533

Sadagopan, S., 284

Saey, T. H., 182

Safavi-Hemani, H., 181

Safer, J. D., 221

Sagi, D., 514

Saha, S., 459, 462

Sahoo, S., 255

Saini, S. M., 466

St. Clair, D., 472

Sairanen, M., 480

Sakai, K., 517

Sakata, H., 360

Sakurai, T., 174

Salamy, J., 522

Salazar, A. M., 524

Saleem, F., 221

Salisbury, D. F., 469

Salomons, T. V., 244

Salpeter, M. M., 28

Salter, M. W., 366

Samara, M. T., 465

Sampson, N. A., 474–475

Sampson, P. D., 136

Sanacora, G., 479

Sanathara, V. A., 193

Sánchez-Sellero, J., 378

Sanders, A. R., 230

Sanders, R. J., 303

Sanders, S., 446

Sandhu, A., 254

Sandin, S., 443

Sani, O. G., 246

Santana, G. L., 486

Santarelli, L., 480

Santini, E., 403

Sanz, C., 428

Sanz, L. R. D., 526

Saper, C. B., 174, 516

Sapolsky, R. M., 255

Sapperstein, S. K., 32

Şar, V., 536–537

Sarachana, T., 444

Saraswat, A., 221

Sarkar, S., 255

Sáry, G., 340

Sasa, M., 479

Sata, R., 470

Sato, S., 209

Satyamurti, S., 381

Savage, C. R., 393

Savage-Rumbaugh, E. S., 303

Savage-Rumbaugh, S., 303

Savic, I., 212, 222, 232, 233, 234

Savica, R., 378

Savin-Williams, R. C., 229

Sawa, A., 466

Sawchenko, P. E., 174

Saxe, R., 76

Saxena, S., 436

Scahill, L. D., 496

Scammell, T. E., 516

Scarr, S., 431, 432

Scerif, G., 425

Schachter, S., 243

Schacter, D. L., 391, 393, 394

Schaefer, M., 368

Schaeffer, M. A., 253

Schafe, G. E., 405

Schaie, K. W., 433, 434, 435

Schank, D., 181

Schank, J. C., 212

Schapiro, A. C., 402–403

Schapiro, M. B., 493

Scharff, C., 305

Schauer, G., 139

Scheele, D., 213

Scheibel, A. B., 423

Schein, S. J., 343

Schelter, B. O., 411

Schenck, C. H., 521, 522

Scherag, S., 193

Scherf, S., 341

Scherr, P. A., 406

Scherrer, G., 355

Scheuer, T., 28

Schiff, N. D., 526

Schildkraut, J. J., 476

Schiller, D., 405, 489

Schiller, P. H., 337

Schindler, S., 484

Schirger, A., 254

Schirmer, B., 515

Schliemman, A. D., 421

Schlötzer-Schrehardt, U. M., 314

Schmidt, A. M., 314

Schmidt, B. P., 324

Schmidt, S. L., 186

Schnakers, C., 526

Schneider, G. E., 80

Schneiderman, I., 213

Schnider, A., 414, 533

Schobel, S. A., 466

Schober, M. E., 78

Schoene-Bake, J.-C., 250

Schoenfeld, D., 302

Schoenfeld, M. A., 168

Scholte, S., 346

Schramm, W. F., 140

Schreiber, R., 478

Schreiweis, C., 306

Schubert, A.-L., 435

Schuckit, M. A., 153

Schuetze, H., 394

Schuhmann, T., 525

Schull, W. J., 76

Schulsinger, F., 459, 470

Schulte-Rüther, M., 191

Schultz, P. G., 12

Schultz, R., 55, 425

Schultz, W., 194, 395

Schüttler, R., 458

Schwartz, B. L., 317, 320, 344

Schwartz, J. H., 316

Schwartz, J. M., 7, 493, 494

Schwartz, M., 226

Schwartz, M. S., 301

Schwartz, M. W., 177

Schwartz, R., 375

Schwartz, S., 435

Schwartz, W. J., 507, 508

Schwarz, A., 530

Schwärzler, F., 481

Schweber, N., 143

Scoles, M. T., 132

Scott, E. M., 170

Scott, T. R., 169, 171

Seckl, J. R., 209

Sedaris, D., 493

Sedlak, T. W., 466

Seeck, M., 361

Seeley, R. J., 177

Seeman, P., 463, 464

Segal, N. L., 431

Seiger, R., 222, 223

Sejnowski, T. J., 44, 334

Sekiguchi, A., 256, 490

Selfe, L., 445

Selkoe, D. J., 409, 410

Sellers, E. W., 526

Selten, J., 470

Sendt, K.-V., 466

Senghas, A., 299

Senju, A., 440

Sepkowitz, K. A., 140

Sergent, C., 525

Sergio, L. E., 299

Servick, K., 35

Seth, A. K., 527

Seth, M., 254

Sevcik, R. A., 303

Sevigny, J., 411

Seward, R., 36

Shadmehr, R., 380

Shadrina, M., 475

Shaffery, J. P., 514

Shah, A., 381

Shah, G. M. S., 469

Shah, P., 434

Shaham, Y., 146

Shalev, A. Y., 490

Shallice, T., 533

Sham, P. C., 471

Shankland, S., 1

Shapiro, A., 512

Shapiro, C. M., 513

Shapiro, M. L., 396

Sharp, T. A., 186

Shen, A., 246

Shenton, M. E., 469

Shepard, R. N., 330

Sheps, S. G., 254

Sherman, D. L., 380

Sherman, G. D., 263

Sherman, R. A., 229

Sherrard, R. M., 444

Sherva, R., 153

Sherwin, B. B., 204, 205

Sheth, S. A., 494

Shi, G., 518

Shi, Z., 205

Shibata, D. K., 300

Shibutani, H., 360

Shifren, J. L., 204, 205

Shima, K., 373, 375

Shimokochi, M., 207

Shimura, T., 207

Shin, L. M., 490

Shirneshan, E., 78

Shiue, I. J., 410

Shohamy, D., 191

Shott, M. E., 194

Shouse, M. N., 518

Shriver, M., 208

Shroads, E., 287

Shuai, Y., 404

Shulgin, A., 142

Shulman, G. L., 529

Shulman, L. M., 205

Shuman, M., 340

Siapas, A. G., 402

Siclari, F., 513

Siegel, B., 426

Siegel, J. M., 518

Siegel, S., 132

Siegelbaum, S. A., 28, 31, 36, 316

Siemens, Y., 262

Siepel, A., 11

Siever, L. J., 477

Siggins, G. R., 135

Sigmundson, H. K., 227

Signoret, J.-L., 342

Silber, M. H., 521

Silbersweig, D. A., 469

Silinsky, E. M., 140

Silove, N., 442

Silva, A. J., 401

Silverman, M. S., 96, 328

Simmons, W. K., 110

Simner, J., 346

Simon, E., 165

Simon, T., 420

Simonsen, M., 446

Simos, P. G., 301

Simpson, J. L., 225

Sinclair, H., 492

Singal, G., 341

Singer, J. E., 243

Singer, T., 260

Singer, W., 75, 469, 527

Singla, N., 255

Singley, A. T., 434

Sinha, A. K., 259

Sinha, P., 339, 341

Siniscalco, D., 445

Sinton, C. M., 174

Sivian, L. J., 276

Sjöstrand, L., 486

Sjöström, L., 189

Skaggs, W. E., 402

Skoog, I., 179

Skorpen, F., 366

Skre, I., 461

Skudlarski, P., 341

Sleser, I., 512

Slijper, F. M. E., 226

Slimp, J. C., 207

Sloan, K. R., 314

Slob, A. K., 232

Slominsky, P. A., 475

Small, S. A., 406

Smalley, S. L., 446

Smallish, L., 447

Smeets, P. A. M., 175

Smeets, T., 263

Smetana, G. W., 187

Smith, A. D., 435

Smith, A. P., 254

Smith, C., 514

Smith, C. N., 395

Smith, D. H., 24

Smith, D. M., 396, 467

Smith, D. W., 76, 136

Smith, E. S., 218, 221

Smith, G. P., 176

Smith, J., 184

Smith, M. A., 380

Smith, M. J., 435

Smith, M. T., 518

Smith, P., 420

Smith, P. H., 140

Smith, S. D., 306

Smith, S. L., 28

Smith, T., 266

Smucny, J., 469

Snowball, A., 434

Snowdon, D. A., 413

Snyder, A. P., 530

Snyder, A. W., 445

Snyder, A. Z., 296

Snyder, L. H., 360

Snyder, S. H., 42, 97, 139, 140, 466, 483

So, K. F., 402

Söderlund, J., 471

Soldati, A., 305

Solet, J. M., 511

Solms, M., 533

Solomon, J., 339

Song, A. W., 105

Song, H., 80

Sonnenschein, D., 511

Sörensen, H. J., 472

Soria, V., 476

Sormanni, P., 408

Sotiriadis, A., 81

Soto-Otero, R., 378

Sowell, E. R., 76

Spalding, K. L., 80

Sparing, R., 106

Spearman, C., 426

Speciale, S. G., 514

Spector, J. A., 146

Spelke, E., 426–427

Spence, C., 374

Spence, S. A., 531

Spencer, K. M., 469

Sperling, R. A., 407

Sperry, R. W., 80

Spetter, M. S., 175

Spiegel, D., 255

Spiers, M. V., 21

Spillantini, M. G., 377, 378

Spinelli, L., 361

Spinney, L., 111

Sprengelmeyer, R., 377

Spreux-Varoquaux, O., 486

Spring, B., 13, 462

Spritzer, M. D., 205

Spurzheim, J. G., 6

Squire, L. R., 376, 391, 392, 393, 395, 414

Srinivasan, R., 287

Srinivasan, S., 462

Sripada, C. S., 261

Sriram, S., 382

Stacy, M., 378

Stahre, M., 134

Stanescu, R., 427

Stanford, A., 531

Stankovic, K. M., 285

Stanley, B. G., 173

Stanley, G. B., 334

Stanton, B. A., 277

Stark, E. L., 404

Stark, S. M., 404

Stárka, L., 205

Starr, C., 370

Starr, J. M., 410

Staton, R. D., 233

Stäubli, U. V., 400

Stebbins, W. C., 304

Steele, D. J., 486

Steele, J. B., 493

Steffen, K. K., 180

Stein, J., 296

Stein, J. L., 429

Stein, M. B., 518

Stein, P. K., 180

Stein, Z. A., 185

Steinberg, E. E., 104

Steinglass, J. E., 191

Steinhauer, S., 154

Steinman, J. L., 364

Steinmetz, M. A., 398

Stellar, E., 163

Stellar, J. R., 163

Stellflug, J. N., 207

Stephan, F. K., 508

Stephens, D. N., 134

Stepper, S., 244

Steriade, M., 517

Sterling, P., 331

Stern, J. S., 187

Stern, Y., 406, 413

Sternbach, R. A., 258

Sternberg, R. J., 421

Sternson, S. M., 173, 174

Stevens, K. E., 469

Steyaert, J., 443

Stickgold, R., 399, 514, 515

Stiffler, J. S., 475

Stinson, F. S., 151

Stoessel, P. W., 7, 493

Stokes, A., 180

Stokhof, M., 494

Stoller, R., 223

Stopper, C. M., 249

Stormshak, F., 207

Strack, F., 244

Strait, D. L., 299

Strand, S., 420

Strandqvist, A., 226

Strang, J., 150

Stratigopoulos, G., 183

Streissguth, A. P., 76, 136

Striegel-Moore, R., 181

Strober, M., 193

Stuart, D. G., 371

Studdert-Kennedy, M., 304

Studer, B., 249

Studte, S., 402

Stunkard, A. J., 170

Sturla, E., 224

Stuss, D. T., 531

Suchan, B., 191

Suddath, R. L., 467

Suddendorf, T., 534

Suga, N., 279, 287

Sullivan, P. F., 190, 192, 460, 475

Sumi, S. M., 76

Sun, D., 120

Sun, X., 175

Sunaert, S., 344

Sundman, M., 105

Supa, M., 290

Surat, P., 100

Surén, P., 443

Susser, E., 185, 472

Susser, M. W., 185

Suthers, R. A., 303

Sutin, A. R., 255

Sutton, S. R., 139

Suvisaari, J. M., 458

Suzdak, P. D., 149

Suzuki, A., 32

Svensson, M., 78

Svensson, T. H., 140

Swaab, D. F., 221, 222, 232, 233, 234

Swann, J., 205

Swanson, J. M., 146

Swanson, L. W., 146

Swartz, K. J., 28

Swayze, V. W., II, 462

Swedo, S. E., 493, 495

Sweeney, K., 169

Sweeney, M., 170

Swerdfeger, A. L., 444

Swift, W. J., 364

Switkes, E., 96, 328

Sylvester, C. M., 491

Syngeniotis, A., 339

Szabuniewicz, C., 252

Szalavitz, M., 151

Szeszko, P. R., 493

Szuajderman, S., 36

Tabakoff, B., 135

Tabrizi, S. J., 381

Taca, A., 150

Tadic, A., 488

Taggart, R., 370

Taira, M., 376

Takahashi, E., 441

Takahashi, J. S., 510, 511

Takao, M., 510

Takaoka, Y., 360

Takayanagi, Y., 456

Talaei, A., 483

Talaga, M. C., 465

Talairach, J., 375

Tam, N., 165

Tamietto, M., 342

Tamura, M., 303

Tanabe, J. L., 469

Tanaka, K., 340, 341

Tanaka, M., 359

Tanaka, Y., 259

Tanda, G., 143

Tang, C., 426

Tang, M., 175, 406

Tanila, H., 396

Tanious, M., 35

Tanji, J., 373, 375

Tank, D. W., 99

Tanne, D., 514

Tanner, C. M., 377

Tannock, R., 449

Tansey, E. M., 371

Tanskanen, A. J., 458

Tao, H. W., 284

Tarr, M. J., 341

Tasker, R. R., 259, 530

Tatsch, K., 449

Tatton, W. G., 377, 378

Taub, E., 527

Taylor, C. S. R., 360, 376

Taylor, D. J., 518

Taylor, D. N., 255

Taylor, G., 469

Taylor, L. E., 444

Taylor, R. C., 287

Taylor, S., 262, 494, 495

Taylor, V. H., 188

Teevan, R. C., 162

Teichert, R. W., 29

Tejada-Vera, B., 407

Telzer, E. H., 249

Temple, E., 256

Ten Eyck, G., 80

te Nijenhuis, J., 430

Tepas, D. I., 506

Teplansky, R., 140

Terburg, D., 263

Terracciano, A., 255

Terrace, H. S., 303, 427

Terribile, M., 224

Terwilliger, E. F., 213

Tessier-Lavigne, M., 71, 74

Tessmar-Raible, K., 509

Teuber, H.-L., 390

Thach, W. T., 376–377

Thakor, N. V., 380

Thaler, L., 290, 291

Thallmair, M., 80

Thambisetty, M., 409

Theberge, A. M., 146

Therrell, B. L., 225

Thibaut, F., 205

Thiele, A., 339

Thier, P., 339

Thigpen, C. H., 535

Thioux, M., 244

Thiran, J.-P., 281

Thomas, P., 497

Thomas, R., 446

Thompson, J. C., 339

Thompson, P. M., 473

Thompson, R. F., 377

Thompson, W. L., 339

Thomson, H., 526

Thomson, S. N., 346

Thorell, L. G., 335

Thornhill, R., 432

Thornton, J., 176

Thornton, L. M., 192

Thyme, S. B., 461

Tian, B., 280

Tibshirani, R. J., 529

Tierney, A. T., 299

Tijms, J., 297

Tikhonov, A., 339

Tilleskjor, C., 470

Tillisch, K., 78

Tishby, O., 36

Tisserand, D. J., 435

Tobey, E. A., 285

Tobi, E. W., 185

Tobias, K. G., 479

Tobler, I., 507

Toda, M., 463

Todd, J. J., 530

Toga, A. W., 76, 261

Tohen, M., 478

Tolin, D. F., 495

Tomasi, D., 188

Tomedi, L. E., 135

Tomer, R., 99

Tonegawa, S., 80, 401–402

Tong, F., 331, 527

Tong, J., 142

Tong, L., 285

Toni, N., 402

Tononi, G., 403, 481, 514, 515, 525

Tootell, R. B. H., 96, 97, 328

Topol, A., 472

Torgersen, S., 461

Torgerson, C. M., 524

Torii, M., 55

Torres, F., 76

Torrey, E. F., 467, 470

Toshitani, K., 458

Touhara, K., 211

Townsend, J., 377

Trace, S. E., 192

Tracey, I., 365, 366

Tracy, D. K., 466

Tracy, T. E., 409

Trainor, B. C., 263

Traish, A. M., 205

Tranel, D., 58, 242, 246–247, 294, 341, 342

Träskman, L., 486

Trautmann, A., 42

Trautmann, S., 456

Treffert, D. A., 445

Tregellas, J. R., 469

Treger, J., 104

Trenkner, S. W., 134

Trepanowski, J. F., 180

Triebel, K., 434

Trifilieff, P., 149

Tripp, G., 449

Trudeau, L.-É., 41

Trulson, M. E., 516

Trumbo, M. C., 106

Tsai, G., 135

Tsai, S.-J., 486, 487, 488

Tsankova, N., 462

Tsay, R., 187

Tschanz, J., 435

Tsend-Ayush, E., 181

Tsivkin, S., 426–427

Tsuang, M. T., 12, 459

Tsujino, N., 174

Tucker-Drob, E. M., 429

Tuiten, A., 205

Tulving, E., 531

Tun, H. M., 189

Turban, J. L., 228

Turel, M., 36

Turkheimer, E., 431

Turnbull, O., 533

Turner, M. S., 533

Turner, R. C., 171

Turton, A. J., 154

Tuten, W. S., 324

Tuvblad, C., 264

Twenge, J. M., 229

Twiss, K. C., 167

Tymula, A., 249

Tyrrell, D. A., 254

Tyrrell, G., 462

Uchino, B. N., 256

Uddin, L. O., 524

Udry, J. R., 205

Ugurbil, K., 334

Uhl, G. R., 2, 306

Uhlhaas, P. J., 469

Ujike, H., 229

Ulanovsky, N., 290

Ullian, E. M., 32

Ullman, M. T., 302

Uncapher, M. R., 527

Underwood, M. D., 479

Ungerleider, L. G., 338, 339, 345, 395

Uno, H., 255

Unterburger, E., 344

Urban, L. A., 361

Urbancic, M., 488

Vaaga, C. E., 41

Vagell, M. E., 216

Vaina, L. M., 339, 343, 344

Vainik, U., 184

Vaisvaser, S., 258

Valagut, G., 488

Valenstein, E. S., 59

van Anders, S. M., 209, 210

van Buchem, M. A., 434

van den Brand, R., 82

van den Brink, W., 148

van den Heuvel, O. A., 518

Van de Poll, N. E., 207

van der Kouwe, A., 441

Van der Linden, A., 280

van der Veen, F. M., 435

Vanderweele, D. A., 169

Van Der Werf, Y. D., 518

Vandlen, R., 188

Van Dongen, H. P. A., 513
van Dorp, C. F., 509
Van Eerdewegh, M., 475
Van Essen, D. C., 44, 345
Van Hecke, P., 344
van Holstein, M., 249
van Honk, J., 263
Van Horn, J. D., 60, 524
Van Horsen, G. W., 409
van Meer, G., 24
van Os, J., 470
van Praag, H., 402
Van Soest, P. J., 168
Van Someren, E. J. W., 518
Van Wyk, P. H., 229
Vargha-Khadem, F., 306
Varki, A., 121
Vauclair, J., 304
Vaughn, A. A., 256
Vauzour, D., 406
Vecchi, G., 408
Veitia, R., 223

Veltman, D. J., 221, 222

Veltman, J. A., 437

Vendrell, J., 182

Vendruscolo, M., 408

Venter, J. C., 11

Verbalis, J. G., 165

Verbene, A. J. M., 175

Verhoye, M., 280

Vernes, S. C., 306

Vernet, M., 344

Verney, E. L., 170

Veroude, K., 264

Verstraten, F. A. J., 338

Vgontzas, A. N., 518

Viana, J., 462

Vick, S.-J., 305

Vidal, C., 473

Vidyasagar, T. R., 529

Vierboom, Y. C., 180

Viergever, M. A., 175

Vigil, O., 496

Vignolo, L. A., 300

Vikingstad, E. M., 298

Vilain, E., 231, 232

Villafuerte, S., 153

Villalobos, M. E., 440

Vinay, L., 371

Viñuela, A., 472

Viola, A., 253

Virkkunen, M., 262, 263

Visscher, P. M., 461

Visser, S. N., 446, 496

Vissers, L. E. L. M., 437

Vissia, E. M., 536

Voelker, D. R., 24

Vogel, G., 60

Vogel, G. W., 481

Vogels, R., 340

Voineagu, I., 445

Volk, H. E., 443

Volkow, N. D., 137, 143, 146, 181, 188

Vollenweider, F. X., 141

Volman, S. F., 303

von Bartheld, C. S., 22

von Cramon, D., 343

von der Heydt, R., 330, 335

VonKaenel, S., 186

Vonlanthen, A., 443

von Ranson, K., 194

von Stumm, S., 429

Vora, C., 181

Voracek, M., 424

Vorel, S. R., 146

Voruganti, L. N. P., 464

Voss, P., 76

Vosshall, L. B., 211

Voyer, D., 218, 226

Voyer, S., 218

Vrenken, H., 518

Vu, E. T., 304

Vul, E., 110

Wada, J. A., 300

Wade, J. A., 405

Wade, T. D., 192

Waechter, R., 536

Wager, T. D., 490

Wagner, A. D., 108, 391

Wagner, D., 141

Wagner, H. J., 382–383

Wahl, S., 185

Wakefield, A. J., 116, 444

Wald, G., 323

Wald, M. M., 79

Waldman, I. D., 432

Walker, E. F., 459, 473

Walker, F. O., 381

Walker, M. F., 357

Walker, M. P., 182

Walkoff, L., 134

Wall, P. D., 364

Wall, T. L., 153

Wallace, G., 432

Walsh, A. E., 488

Walsh, B. T., 190, 191

Walsh, M. L., 262

Waltes, R., 264

Wan, F.-J., 135

Wang, A., 378

Wang, B., 30, 231

Wang, C. Y., 182

Wang, G.-J., 146, 188

Wang, H., 470

Wang, H. X., 378

Wang, J., 219, 449

Wang, J. C., 153

Wang, O., 187

Wang, P. S., 475

Wang, R., 306, 441

Wang, S., 247

Wang, S.-H., 394

Wang, S.-M., 412

Wang, X., 284, 285, 365

Wang, Z., 80, 212, 213

Warburton, V. L., 209

Ward, B. W., 229

Wardlaw, S. L., 364

Ware, M., 427

Warner, L. A., 153

Warner, M. H., 232

Warner-Czyz, A. D., 285

Warren, S., 359

Wasserman, R., 314

Wasserstein, J., 448

Watanabe, N., 518

Watanabe, T., 443

Waterland, R. A., 185

Waters, A. J., 139

Watkins, L. R., 364

Watkinson, B., 143

Watson, C. G., 470

Watson, H. J., 192

Watson, J. D., 8

Watson, N. V., 209

Waxman, S. G., 31, 366

Way, B. M., 260

Webb, D. M., 326

Webb, E. M., 434

Webb, W. B., 506

Weber, B., 250

Weber, W. A., 78

Weeks, D., 479

Wegner, D. M., 258

Wehr, T. A., 481, 482

Wei, X., 120

Weinand, J. D., 221

Weinberg, M. S., 229

Weinberg, R. A., 430, 431, 432

Weinberger, D. R., 467, 468, 473

Weinstein, S., 355

Weir, A. A. S., 428

Weisse, C. S., 253

Weisskopf, M. G., 449

Weitzman, E. D., 519

Wekerle, H., 382

Welch, B. T., 134

Welch, J. M., 495

Wells, B. E., 229

Wells, J. E., 488

Welner, J., 459

Weltzin, T. E., 191

Wen, W., 435

Wender, P. H., 448, 459, 460

Wennberg, P., 152

West, D. B., 176

Westbrook, G. L., 41

Westenberger, A., 377

Westerberg, C. E., 515

Weston, N. M., 120

Weuve, J., 406

Wever, E. G., 281, 282, 284

Wheaton, K. J., 339

Wheeler, M. A., 531

Wheeler, M. E., 395, 396

Whidbee, D., 515

Whipple, B., 209, 364

Whitam, F. L., 234

White, C. D., 427

White, N. M., 397

White, S. D., 276

Whiten, A., 534

White-Schwoch, T., 299

Whiteside, S. P., 493

Whitfield, S., 469

Whitney, D., 343

Wicherts, J. M., 424

Wichmann, T., 376, 380

Wickelgren, I., 399

Wickens, J. R., 449

Wiebe, V., 326

Wiegand, J., 479

Wierenga, C. E., 191

Wierzynski, C. M., 402

Wiesel, T. N., 326, 332, 333, 334, 335

Wiggs, C. L., 395

Wikler, K. C., 216

Wilbert-Lampen, U., 254

Wilcock, G. K., 411

Wilens, T. E., 447

Wiles, N., 478

Wilkins, D., 142

Wilkinson, M., 441

Willerman, L., 55, 425

Williams, G., 187

Williams, G. B., 138, 153–154

Williams, H., 304

Williams, J. H. G., 534

Williams, K., 442

Williams, N. M., 448

Williams, R. W., 75

Williams, T. J., 233

Willie, J. T., 174

Willwerth, J., 523

Wilson, A., 532

Wilson, A. C., 12

Wilson, F. A., 339

Wilson, G. D., 233

Wilson, J. R., 204

Wilson, M., 219

Wilson, M. A., 396, 402

Wilson, R. I., 142–143

Win, A. K., 476

Windmill, J. F. C., 275

Wingard, D. L., 518

Wingfield, J. C., 232

Winkielman, P., 110, 245, 440

Winocur, G., 341

Wise, R. A., 138, 145, 181

Wise, S. P., 398

Witelson, S. F., 232, 233, 423

Wittchen, H.-U., 78, 456, 474–475

Witte, H., 527

Wittert, G. A., 205

Witthoft, N., 343

Witztum, E., 205

Wolf, L. E., 448

Wolff, J. J., 45, 441

Wolff, P., 459

Wollberg, Z., 279

Wolpert, D. M., 372, 376

Won, E., 483

Wong, K., 463

Woo, S.-H., 354

Wood, D. L., 254

Wood, S. H., 181

Woods, B. T., 473

Woods, C. G., 74

Woods, S. C., 174, 176

Woodworth, R. S., 13

Woolf, C. J., 366

Woollett, K., 423

Worley, P. F., 483

Wray, N. R., 461

Wright, J. D., 182

Wright, M. J., 429

Wright, R. O., 449

Wright, V. L., 150

Wu, C.-S., 143

Wu, G., 284

Wu, J. C., 481

Wurtman, J. J., 187, 482

Wurtman, R. J., 187, 482

Wuttke, D., 181

Wyatt, H. R., 181

Wyatt, J. R., 285

Wyatt, R. J., 80, 467

Wyatt, T. D., 212

Wynn, K., 427

Wysocki, C. J., 211

Xia, X., 526

Xiang, A. H., 184

Xiao, C., 100

Xiao, Z., 279, 287

Xie, L., 515

Xu, H., 180

Xu, J., 114

Xu, L., 79

Xu, Y., 519

Yacoub, E., 334

Yam, P., 419

Yamada, M., 480

Yamanaka, A., 174, 175

Yamane, S., 341

Yan, H., 444

Yanagisawa, M., 174

Yanagisawa, T., 368

Yang, C. F., 204, 207

Yang, J. E., 371

Yang, W., 183

Yang, Y., 261

Yang, Y. C., 255

Yang, Z., 212

Yanowitch, R. N., 261

Yap, G. S., 373, 374

Yarbrough, C. J., 117

Yau, K.-W., 510

Yau, S. Y., 402

Yauk, C. L., 154

Ye, L., 99

Yeni-Komshian, G. H., 300, 304

Yi, C.-X., 175

Yildirim, E., 510

Yin, Y., 175

Yip, M., 285

Yip, P. K., 78

Ylönen, H., 211

You, J. S., 488

Youdim, M. B. H., 377

Young, E., 106

Young, L. J., 212, 213

Young, M. P., 341

Yousry, T. A., 533

Yu, C. J., 449

Yu, M., 486

Yu, X., 41

Yücel, M., 143

Yuste, R., 36

Zack, J. A., 255

Zada, D., 515

Zagoory-Sharon, O., 213

Zaheer, J., 458

Zai, G., 488

Zai, L., 82

Zalesky, A., 143

Zambreanu, L., 366

Zametkin, A. J., 449

Zandieh, S., 255

Zanos, P., 477

Zanzotto, G., 231

Zarate, C. A., 483

Zaslavsky, A. M., 474, 488

Zatorre, R. J., 76

Zebhauser, P. T., 344

Zec, R. F., 467, 468

Zeiler, M., 424

Zeki, S., 340, 342, 343, 345

Zepelin, H., 506

Zerbo, O., 443

Zhang, F., 104

Zhang, H., 406

Zhang, H. G., 488

Zhang, J., 114, 175, 326, 506

Zhang, L., 449, 489, 490

Zhang, L. I., 284

Zhang, S. M., 383

Zhang, W., 114, 175

Zhang, X., 134

Zhang, Z., 257

Zhang-James, Y., 264

Zhao, L., 412

Zhao, Z., 393

Zhong, Y., 404

Zhou, J. N., 221, 222, 232

Zhou, M., 433

Zhou, W., 233

Zhou, Y., 79

Zhou, Z. J., 41

Zhou-Hao, L., 78

Zhu, Q., 341

Zihl, J., 343

Zillmer, E. A., 21

Zimmerman, C. A., 165, 166

Zion Golumbic, E. M., 287

Zohar, J., 494

Zola, S. M., 392

Zola-Morgan, S., 392, 414

Zollinger, S. A., 303

Zoloth, S. R., 304

Zonderman, A. B., 255

Zou, K., 484

Zubenko, G. S., 475, 486

Zubenko, W. N., 475

Zuberbühler, K., 305

Zubin, J., 13, 462

Zuckerman, M., 163

Zuker, C. S., 168

Zukin, S., 33

Zweifel, L. S., 246

SUBJECT INDEX

Abecedarian Project, 431

Aberrant salience hypothesis, 463

Ablation, 105

Ablatio penis, 226–228

Absolute refractory period, 30

Absorptive phase, 172

ACC. *See* Anterior cingulate cortex (ACC)

Accommodation, 316

Acetylcholine, 38

Acetylcholinesterase, 38, 381, 382 (figure)

Acral lick syndrome, 495

Action potential, 27–28, 27 (figure)

Activating effects, 215

Active transport, 68 (figure)

Acute, 459

Adaptive emotion, pain as an, 258–260

Adaptive hypothesis, 506

Adaptive response, stress as an, 251–253

Addiction, 144–151

definition, 130

genes and, 152–155

research, implications of, 154

role of reward, 145

synaptic plasticity and, 146–147

treating, 147–151

See also Drug(s)

Adequate stimulus, 275–276, 314

ADHD. *See* Attention-deficit/hyperactivity disorder (ADHD)

Adipose tissue, 172

Adolescence, and schizophrenia, 473

Adolphine, 149

Adoption study, 112

Adrenoleukodystrophy (ALD), 115

Affective aggression, 260

Affective (mood) disorders, 457 (table), 473–487

antidepressants and, 480

bipolar and related disorders, 457 (table), 473–475, 483–486

depression, 457 (table), 473–488, 495

electroconvulsive therapy (ECT) and, 479

heredity and, 475–476
major depressive disorder (MDD), 457 (table), 474
mania, 474, 479, 481, 483, 485 (figure)
monoamine hypothesis of depression, 476–478
neural plasticity, 480
neurological anomalies in, 483–486
rhythms and, 481–483
seasonal affective disorder (SAD), 457 (table), 481–483
suicide and, 486–487
Agency, 530
Aggression, 260
biological origins of, 260–265
brain's role in, 260–261
definition, 260
environment and, 264–265
heredity and, 264–265
hormones and neurotransmitters in, 261–264
See also Emotion
Aging
intelligence and, 433–436

memory and, 406
Agnosia, 340
Agonists, 42, 130
Agonist treatments, 148–149
Agouti-related protein (AgRP), 173
Agranulocytosis, 465
Agraphia, 295
AIC (anterior insular cortex), 249–251
Alcohol/alcoholism, 133–136, 143, 145, 148, 148 (figure)
genetics and, 152–154
treatment, 149–150, 151 (table)
See also Addiction; Depressants
Alexia, 295
Alleles, 9
All-or-none law, 29
Alpha waves, 511
Alzheimer, Alois, 406
Alzheimer's disease, 79, 406–413
brain plaques and tangles, 407–409
detecting, 412–413

Down syndrome and, 409

environment and, 409–410

heredity and, 409–410

resistance to (reserve hypothesis), 413

treatment of, 410–412

Amacrine cells, 317

Amino acids, 171

Amnesia, 391–392

Amphetamines, 138–139

Amplitude, 275–276

Amygdala, 145 (figure), 207, 245 (figure), 246–247, 246 (figure)

Amyotrophic lateral sclerosis (ALS), 419

Analgesic, 131

Androgen insensitivity syndrome, 224

Androgens, 204

Angiotensin II, 165–166, 166 (figure)

Angular gyrus, 292 (figure), 295

Animal research, 117–119

Annese, Jacopo, 392

Anomia, 293

Anorexia nervosa, 190–194

See also Eating disorders

ANS (autonomic nervous system), 69–71, 72 (figure)

Antagonistic muscles, 369–370

of the upper arm, 370 (figure)

Antagonists, 42, 130

Antagonist treatments, 149

Anterior, 57

Anterior cingulate cortex (ACC), 249–251, 524 (figure)

Anterior cingulate gyrus, 251 (figure)

Anterior commissure, 54 (figure), 63

Anterior dorsolateral prefrontal cortex, 491 (figure)

Anterior hypothalamus, 164 (figure)

Anterior insula, 491 (figure)

Anterior insular cortex (AIC), 249–251

Anterograde amnesia, 391

Antiadrenergic side effects, 465

Anticholinergic side effects, 465

Antidepressants, 476–477, 480

Antidrug vaccines, 149

Antipsychotics, 465, 469, 478, 483, 494

Antisense RNA, 114

Anvil, 277 (figure), 278

Anxiety, trauma, and stress-related disorders, 457 (table), 487–492, 491 (figure)

brain anomalies, 490–491

generalized anxiety, 457 (table), 488–489

heredity and, 488

panic disorder, 457 (table), 488–489

phobia, 457 (table), 488–489

posttraumatic stress disorder (PTSD), 457 (table), 489, 490 (figure)

Anxiolytic, 133

Aphasia, 292–293, 297–299

Apotemnophilia. *See* Body integrity identity disorder

Appetite, effects of nicotine and marijuana on, 178

See also Hunger; Obesity

Applications. *See* Further look

A Quiet Place (movie), 273

Arcuate fasciculus, 292 (figure)

Arcuate nucleus (ARC), 164 (figure), 173, 173 (figure)

Area postrema, 171

Aristotle, 4, 92

Aromatization, 216

Arousal, sexual, 202–204

Arousal theory, 163

Artificial neural networks, 44

ASD. *See* Autism spectrum disorder (ASD)

Asher, Julian, 346

Asperger syndrome. *See* High-functioning autism

Aspiration, 105

Association areas, 59

Associative long-term potentiation (LTP), 400, 400 (figure)

Astrocytes, 32, 39 (figure)

Atonia, 512

Attention, 528–530

Attention-deficit/hyperactivity disorder (ADHD), 446–450

    brain anomalies in, 447–448

    environment and, 449–450

    genes and neurotransmitters, 448–449

Atwood, Eden, 224

Atypical (second-generation) antipsychotics, 465, 478

Audiogram (human), 276 (figure)

Auditory cortex, 56 (figure), 61, 279–281

Auditory mechanism, 276–280, 281 (figure)

Auditory nerve, 277 (figure), 279, 280 (figure), 281–282, 284

Auditory object, 287

Auditory scene, 287 (figure)

Autism spectrum disorder (ASD), 438–446

- autistic savants and high-functioning autism, 445–446
- biochemical anomalies and, 442
- brain anomalies and, 440–441
- childhood vaccines and, 444
- cognitive and social impairment, 439–440
- environment and, 442
- heredity and, 443–445

Autistic savants, 445–446

Autobiographical memory, 397

Auto-brewery syndrome, 134

Autoimmune diseases/disorders, 253, 381–383

Autonomic nervous system (ANS), 69–71, 72 (figure)

Autonomic involvement in emotion, 242–245

Autoradiography, 95–96, 97 (figure)

Autoreceptors, 39

Aversive treatments, 149

Awareness, 525–528

Ax, Albert, 116, 243

Axoaxonic synapses, 38–39

Axodendritic synapses, 38

Axon, 22, 23 (figure), 31 (figure)

Axon hillock, 23 (figure), 35

Axon terminals, 22–23, 33 (figure), 36 (figure)

See also Terminals

Axosomatic synapses, 38

Bacteriodetes, 182

Barbiturates, 136

Baron, Rick, 404

Basal forebrain, 517, 517 (figure)

Basal ganglia, 376–377

Basal metabolism, 186

Basic rest and activity cycle, 511

Basilar membrane, 278, 279

Bath salts, 139

B cells, 253

Becker, Anne, 192

Behavior

definition, 2

physical model of, 4–5

See also Behavioral neuroscience; Biology of sex and gender; Body senses; Brain; Drug(s); Emotion; Intelligence; Internal states, regulation of; Language; Learning; Memory/memories; Nervous system; Psychological disorders; Sleep; Vision

Behavioral addiction, 147

Behavioral neuroscience, 1–18

definition, 2

electrical brain, 5–6

localization, 6–7

mind-brain problem, 3–4

nature versus nurture, 8–14

origins of, 2–7

physical model of behavior, 4–5

prescientific psychology, 3–4

See also Brain; Nervous System; Research

Benzodiazepines, 136

Berger, Hans, 100

Beta waves, 511

Binaural, 288

Binaural cues, 288

Binder, Elizabeth, 490

Binding, 346

Binding problem, 345

Binet, Alfred, 420

Binge eating disorder, 190–194

See also Eating disorders

Binge-purgers, 190

Binocular rivalry, 529

Biological psychology (biopsychology). *See* Behavioral neuroscience

Biological rhythm, 509

Biology of sex and gender, 201–238

biological determination of sex, 213–217

biological model, social implications of, 234–235

biological origins of gender identity, 220–228

gender-related behavioral and cognitive differences, 217–220

sex as a form of motivation, 202–213

sexual orientation, 228–235

Bipolar cell, 316, 316 (figure)

Bipolar disorder, 457 (table), 473–475, 483–486

Bipolar neuron, 24

Bleuler, Eugen, 458, 458 (figure)

Blindsight, 342

Blind spot, 318

Blood-brain barrier, 68

Blum, Kenneth, 153

Body image, 531–532

Body integrity identity disorder, 361

Body mass index (BMI), 179, 180 (figure), 183 (figure)

Body senses, 353–386

pain, and its disorders, 361–368

posterior parietal cortex, 358–361, 372 (figure), 373

proprioception, 354

skin senses, 354–356

somatosensory cortex, 358–361, 372 (figure)

vestibular sense, 356–357

See also Movement

Bonding, 212–213

Bor, Daniel, 527

Borderline personality disorder, 457 (table), 497

Boring, Edward G., 168

Born This Way (TV series), 437 (figure)

Bradley, Bill, 421

Brain

aggression and, 260–261

breastmilk and, 78

computer chips and interfaces, 84, 375

cortex, 53, 54 (figure)

cranial nerves, 69–70, 70 (figure)

development of, 53 (figure)

electrical, 5–6

functional areas of, 7 (figure)

hydrocephalic, 81 (figure), 438 (figure)

imaging techniques, 106–111

intelligence and, 423–426

interior features of, 62 (figure)

interpreter, 534

lissencephalic, 51, 52 (figure)

lobes and functional areas, 56 (figure)

lobotomized, 58–59, 59 (figure)

major structures and functions, 65–66 (table)

model, growing from stem cells, 111

motor cortex, 56, 58 (figure), 247–249, 359 (figure), 372–376

movement and, 372–377

normal, 52 (figure), 81 (figure)

of three differentmammals, 55 (figure)

phrenologist’s L. M. Fowler’s map of, 7 (figure)

prenatal hormones and, 216

processing speed, 425–426

reserve, 413

size, 424–425

specific abilities and general intelligence, 426–429

split, 534–536

stem, 65, 280 (figure), 516

synaptic plasticity and addiction, 146–147

ventral view of, 70 (figure)

ventricles, 63

views of, 52 (figure), 53 (figure), 54 (figure), 62 (figure), 70 (figure)

visual pathways to, 318–320

See also Behavior; Behavioral neuroscience; Brain activity, measuring and manipulating; Brain anomalies; Disorders; Gray matter; Nervous system; White matter

Brain activity, measuring and manipulating, 100–106

ablation and lesioning, 105

electroencephalography, 100–102

stimulation, recording, and stereotaxic techniques, 102–105

transcranial magnetic stimulation, 105–106

Brain anomalies

anxiety, trauma, and stress-related disorders and, 490–491

attention-deficit/hyperactivity disorder and, 447–448

autism spectrum disorder and, 440–441

Brainbow, 114

Brain stimulation reward, 145

Bray, Charles, 281

Breastmilk, and the brain, 78

Broca, Paul, 6, 292

Broca’s aphasia, 292

Broca’s area, 6, 6 (figure), 56, 56 (figure), 292–293, 292 (figure)

Brown, Alan, 471

BSTc (central subdivision of the bed nucleus of the stria terminalis), 221

“Bubble boy disease,” 91, 92 (figure), 115

Bulimia nervosa, 191–194

See also Eating disorders

Buñuel, Luis, 533

Bush, George W., 121, 421

Caffeine, 140

Cannabinoids, 142–143

Cannabis sativa, 142

Cannon, Walter, 254

Cannula, for microdialysis, 104 (figure)

Capacitance, 31

Cardiac deaths, and stress, 254 (figure)

Cardiac muscles, 369

Carlsson, Arvid, 118

Carnivores, 167

Caro, Isabelle, 191 (figure)

Carter, Howard, 110

Cas-9 enzyme, 115

Case of George Dedlow, The (Mitchell), 532

Case study, 93

Castration, 204–205

Cataplexy, 521, 521 (figure)

Catecholaminergic psychedelics, 141

CAT scans. *See* Computed tomography (CT)

Caudate nucleus, 376 (figure)

Cell(s), 22–32

- amacrine, 317
- B, 253
- bipolar, 316, 316 (figure)
- body (soma), 22, 23 (figure), 24 (table), 26, 30, 34–35, 36 (figure), 37
- complex, 333, 334 (figure)
- endothelial, 68 (figure)
- ganglion, 316, 316 (figure), 326 (figure), 332 (figure), 510 (figure)
- glial, 30–32, 39 (figure), 73, 73 (figure)
- hair, 278

horizontal, 317
immune, 253 (table)
natural killer, 252
olfactory receptor, 211 (figure)
place, 395–396
Schwann, 30–31, 31 (figure)
simple, 333, 333 (figure)
skin, 111
T, 252
See also Neuron(s); Stem cells
Cellular (mobile) phones, 1–2
Central executive network, 524, 524 (figure)
Central nervous system (CNS), 52–69
damage and recovery in, 77–83
forebrain, 53–64
midbrain and hindbrain, 64–66
protecting, 68–69
spinal cord, 66–68
See also Nervous system
Central pattern generator (CPG), 371

Central subdivision of the bed nucleus of the stria terminalis (BSTc), 221

Central sulcus, 56, 56 (figure), 359 (figure)

Cerebellum, 22 (figure), 36, 53 (figure), 62 (figure), 65, 66 (table), 372 (figure), 373 (table), 376–377

Cerebral achromatopsia, 343

Cerebral aqueduct, 64 (figure)

Cerebral cortex. *See* Cortex (cerebral)

Cerebral hemispheres, 53–55

Cerebrospinal fluid, 63, 68 (figure), 193 (figure)

Chemical transmission at the synapse, 33–38

Cheshire cat effect, 529

Chimpanzee brain, 55 (figure), 58

Cholecystokinin (CCK), 176

Chomsky, Noam, 299

Chromosomes, 8–9, 11, 213–216

Chronic, 459

Chronic pain, 365–366

Chronotype, 519

Cingulate gyrus, 62 (figure), 245 (figure)

Circadian rhythm, 481, 507–511, 519 (figure)

Circannual rhythm, 481

Circuit formation, 74

Circuit pruning, 75–76

Cirelli, Chiara, 514

CLARITY, 99

Classical conditioning, 400

Cloninger, Robert, 152

CNS. *See* Central nervous system (CNS)

Cocaine, 137–138, 147 (figure)

Coccaro, Emil, 262

Coccyx, 67

Cochlea, 274, 277 (figure), 280 (figure), 357 (figure)

Cochlear canal, 277 (figure), 278

Cochlear implants, 285–286, 285 (figure)

Cochlear nerve, 277 (figure), 357 (figure)

Cochlear nucleus, 280 (figure)

Cocktail party effect, 287

Codeine, 131

Cognitive functioning. *See* Disorders; Intelligence

Cognitive psychology, 506

Cognitive theory, 243

Coincidence detectors, 289

Color, perception of, 337–346

Color agnosia, 342–343

Color blindness, 327–328

Color coded, 343

Color constancy, 343, 343 (figure)

Color vision, 320–328

color blindness, 327–328

combined theory of, 322–326

opponent process theory, 321–322

trichromatic theory, 320–321

Coma, 526

Communication, within the nervous system, 21–49

cells, 22–32

neuron communication, 32–45

See also Nervous system

Comorbidity, 151

Compensation, 81–82

Complementary colors, 321, 322 (figure)

Complex cells, 333, 334 (figure)

Compulsions, 492

Computed tomography (CT), 106, 106 (figure)

Computer-brain interfaces, 375

Computer chips, and mending the brain, 84

Concordance rate, 113

Conditioned tolerance, 132

Cone snail, 29, 181

Confabulation, spontaneous, 414

Confocal laser scanning microscope, 99

Congenital adrenal hyperplasia (CAH), 224, 224 (figure)

Congenital insensitivity to pain, 258

Consciousness, 522–536

- attention, 528–530
- awareness, 525–528
- determining, 526
- network explanations of, 523–525
- sense of self, 530–536
- *See also* Sleep

Consolidation and retrieval, of memories, 392–395, 402–403

Contrast enhancement, 329–331

Control system, 163

Convoluted, 53

Coolidge effect, 204, 209

Cooper, Martin, 2 (figure)

Copy number variations (CNVs), 461

Corelease, 41

Cornea, 315, 316 (figure), 317 (figure)

Coronal plane, 57 (figure)

Corpus callosum, 54 (figure), 62 (figure), 63, 81

Correlation, 112

Correlational studies, 93–94

Correlation coefficient, 112

Cortex (cerebral), 53–64, 508 (figure)

- drugs and, 133, 136, 137
- intelligence and, 423, 441, 449
- language and, 287, 292 (figure), 294, 297
- learning and, 395, 402, 403
- movement and, 357–361, 372–373
- taste and, 168 (figure)
- vision and, 328, 330, 332–334
- *See also* Gray matter

Cortisol, 242, 251, 263–264

Cotransmission, 41

Crack, 137

Cranial nerves, 69–70

Crick, Francis, 8, 522–523

CRISPR, 115

Cross-fostering, 112

Cryptochromes, 97, 97 (figure)

Crystallized intelligence, 433–434

Cupula, 356, 357 (figure)

Curare, 42

Cytoplasm, 22 (figure)

D2 receptors, 188 (figure)

Dale’s principle, 40

Dali, Salvador, 335

Dallenbach, Karl, 290

Damasio, Antonio, 242

Damasio, Hanna, 60

Darwin, Charles, 4, 12 (figure), 303

Davis, Clara, 169

Deacon, Terrence, 302

de Balzac, Honoré, 129, 130 (figure)

Decade of the Brain, 2

Deception, 117

Declarative memory, 397

Dederich, Charles, 147

Deep brain stimulation (DBS), 379, 380

Default mode network, 435, 491, 524 (figure)

Default sex, 215

Deficiencies. *See* Disorders

Deisseroth, Karl, 99

Delayed match-to-sample task, 373, 398

Delirium tremens, 135

Delta-9-tetrahydrocannabinol (THC), 142–143

Dement, William, 521 (figure)

Dementia, 406

    pugilistica, 79

    with Lewy bodies, 377

Democritus, 4

Dendrites, 22, 23 (figure)

Dendritic spines, 402

Deoxyribonucleic acid (DNA), 8–12, 14, 98 (figure)

Dependence, 130

Depressants, 133–136

alcohol, 133–136

barbiturates and benzodiazepines, 136

Depression, 457 (table), 473–486, 488, 489, 495

long-term depression (LTD), 399

major depressive disorder (MDD), 457 (table), 474

monoamine hypothesis of, 476–478

reactive depression, 473–474

seasonal affective disorder (SAD), 457 (table), 481–483

Dermatomes, 358

Descartes, René, 4, 92

Descending pain inhibition circuit, 364–365, 365 (figure)

Descent of Man and Selection in Relation to Sex, The (Darwin), 303

DeSilva, Ashanthi, 92

Detoxification, 148

De Valois, Russell, 326, 328

Developmental disease, 472–473

de Vivo, Luisa, 515

Dextroamphetamine sulfate, 138

DHA (docosahexaenoic acid), 78

Diabetes, 172, 179, 181

Diabetes gene, 183

Diagnostic and Statistical Manual of Mental Disorders, 5th edition *(DSM-5)* (American Psychiatric Association), 192, 436, 457, 535

Dialects, 303

Dichotic listening task, 279

Diderot, Denis, 290

Diffusion tensor imaging (DTI), 107, 107 (figure)

Digestion, and the two phases of metabolism, 171–173

Digestive process, 171–172

Dihydrotestosterone, 215, 223

Di Lorenzo, Patricia, 42

Disorders

- eating, 190–194, 520
- intelligence, 433–450
- learning, 405–414
- movement, 377–383
- pain, 361–368
- self, 534–536

sleep, 518–521

visual perception, 340–345

See also Psychological disorders; *name of individual disorder*

Dissociative identity disorder (DID), 534–536

Dissociatives, 141

Distributed, 337

Diversity, 11

Dizygotic, 112

DMT (dimethyltryptamine), 141

DNA. *See* Deoxyribonucleic acid (DNA)

Docosahexaenoic acid (DHA), 78

Doctrine of Specific Nerve Energies (Müller), 77

Dominant allele, 9

Dopamine, and eating disorders, 194

Dopamine hypothesis, 463–466

Dorsal, 57 (figure)

Dorsal ACC, 491 (figure)

Dorsal root, 66

Dorsal stream, 280, 338, 339 (figure)

Dorsolateral prefrontal cortex, 467

Doudna, Jennifer, 119

Down syndrome, 409, 437

Dreaming. *See* Sleep

Drive, 163

Drive theory, 163

Drug(s), 129–158

- definition, 129
- depressants, 133–136
- marijuana, 142–144
- opiates and opioids, 131–133
- psychedelic, 141–142
- psychoactive, 130–144
- stimulants, 137–140
- withdrawal, 150
- *See also* Addiction

DTI (diffusion tensor imaging), 107, 107 (figure)

Dualism, 4

Duck-billed platypus, 181

Dull pain, 362

Duncan, John, 423

Duodenum, 171

Dyscalculia, 295

Dyslexia, 295–297, 298 (figure)

Eastwood, Clint, 375

Eating disorders, 190–194

environmental and genetic contributions, 192–193

neurotransmitters, role of, 193–194

sleep-related, 520

See also Internal states, regulation of

Echolocation, 290

Ecstasy (drug), 141

Edge detection, 329–331

Edison, Thomas, 284

EEG. *See* Electroencephalogram (EEG)

Egger, Hubert, 375

Einstein, Albert, 423, 462

Ekman, Paul, 244

Electrical brain, 5–6

Electroconvulsive therapy (ECT), 479, 480

Electroencephalogram (EEG), 100–101, 102 (figure), 109 (table), 512 (figure)

Electroencephalography, 100–102

Electromagnetic spectrum, 314

Electron microscopy, 98–99

Electrostatic pressure, 26

Embryo, 8

Embryonic cells, and Parkinson’s disease, 378, 379 (figure)

Embryonic stem cells, 83, 83 (figure)

Emotion, 241–269

- aggression, biological origins of, 260–265
- autonomic and muscular involvement in, 242–245
- definition, 242
- nervous system and, 242–251
- stress, immunity, and health, 251–260
- *See also* Motivation

Emotional brain, 245–251

Empathy, 212–213

Empiricism, 5, 92

Encapsulated receptors, 355

Encyclopedia of DNA Elements (ENCODE) Project, 11

Endogenous, 132

Endophenotypes, 487

Endorphins, 132, 363

Endothelial cell, 68 (figure)

Endothermic, 164

Enkephalin, 365 (figure)

Environment, 8–9, 12–14

- addiction and, 152
- aggression and, 264–265
- Alzheimer’s disease and, 409–410
- attention-deficit/hyperactivity disorder and, 449–450
- autism and, 443
- eating disorders and, 192–193
- intelligence and, 431–433
- obesity and, 182–185
- schizophrenia and, 470–472
- sexual orientation and, 218, 221, 229, 231

Epigenetic, 184

Epigenetic influences, and sexual orientation, 230–232

Episodic memory, 397

Equipotentiality, 6

Eriksson, Peter, 80

Estradiol, 216

Estrogens, 204, 435

Estrus, 205

Ethics. *See* Research ethics

Etiology, 462

Euphoric, 131

Eustachian tube, 278

Evans, Vyvyan, 302

Event-related potential, 101, 525 (figure)

Excitation and inhibition, 34–36, 36 (figure)

Excitatory postsynaptic potential (EPSP), 35

Excitement phase, 203

Exocytosis, 33, 77

Exercise, and weight loss, 165, 167, 181, 186–187

Experiment, 93

Experimental studies, 93–94

Expressive aphasia, 292

External auditory canal, 277 (figure)

Extinction, of memories, 403

Extracellular fluid, 25 (figure), 26 (figure)

Extrapyramidal effects, 465

Eye, and its receptors, 315–318

Fabrication, in research, 116

Facial motor area, 292 (figure)

Facial nerve, 357 (figure)

Familial, 377

Family study, 111–112

Farina, Dario, 375

Fasting phase, 172–173

Fast-spiking neurons, 30

Fatty acids, 171

Fear erasure, 489

Feedback from the body, role of, 243–245

Feeding signals, summary of, 177 (table)

Female-male differences, 215 (figure), 217–220

Fetal alcohol syndrome, 75, 76 (figure), 136 (figure)

Fetus, 8

Firefox (Thomas), 375

Firmicutes, 182

First-generation antipsychotics, 465

Fissure, 53

Flavor, 171

Fluid intelligence, 434

Flynn effect, 430, 433

Force of diffusion, 26

Forebrain, 53–64, 517

Forgetting, 403–404

Form vision, 328–336

- contrast enhancement and edge detection, 329–331
- Hubel and Wiesel's theory, 332–335
- spatial frequency theory, 335–336

Fornix, 245 (figure)

Fourier, Joseph, 286

Fourier analysis, 286, 286 (figure)

- 46 XX intersex, 224–225
- 46 XY intersex, 222–224

Fourth ventricle, 63

Fovea, 316 (figure), 317

Fox, Michael J., 354, 379, 383

Fragile X syndrome, 438

Frank, Barney, 234, 234 (figure)

Freebase, 137

Freeman, Walter, 58, 59 (figure)

Free nerve endings, 355

Frequency, 275

Frequency analysis, 281–284

Frequency-place theory, 284

Frequency theory, 281

Frequency-volley-place theory, 284

Freud, Sigmund, 137, 148 (figure)

Fritsch, Gustav, 5

Frontal lobe, 56, 56 (figure), 62 (figure)

Frontoparietal network, 491

Fugu (puffer fish), 28

Functional magnetic resonance imaging (fMRI), 108, 108 (figure)

Further look

Agonists and Antagonists in the Real World, 42

Alzheimer’s in a Dish, 408

Antipsychotics and Their Side Effects, 465

Auto-Brewery Syndrome, The, 134

Beyond Cochlear Implants, 285–286

Brainbow Connection, The, 114

Brain-Computer Interfaces, 375

Bug That Causes Road Rage, A, 262

Building a Better Brain, 78

Can Gene Editing Be Regulated?, 120

Case of Phineas Gage, The, 60

Changing Attitudes toward Marijuana, 144

Childhood Vaccines and Autism, 444

CRISPR: A New Tool to Edit Genes, 14

Deep Brain Stimulation and Parkinson's Disease, 380

Determining Consciousness When It Counts, 526

Diabetes, the Duck-Billed Platypus, and the Cone Snail, 181

Enhancing Intelligence and Cognitive Performance, 434

Government Agencies Act to Curb Overdose Deaths, 133

Growing a Model Brain from Stem Cells, 111

GTEx Project Provides New Insight into the Differences between the Sexes, 219–220

How Nicotine and Marijuana Affect Appetite, 178

How Puffer Fish Manage Stress, 252

I Hear a Tree Over There, 290

In the Still of the Night, 520

Legacy of H. M., The, 392

Looking into the Brain, 99–100

Mending the Brain with Computer Chips, 84

Microtubules Move Neurons Along Their Way, 74

Neural Bases of Visual Illusions, 330

Neurocriminology, Responsibility, and the Law, 265–266

Neuron Type Found Only in Humans, A, 35

New Treatment for Pain: Botox, A, 132

Obesity Alters Your DNA, 185

OCD and Mysophobia, 492–493

Of Love, Bonding, and Empathy, 212–213

One Aftermath of Disaster Is Stress-Related Brain Damage, 256

Pets May Provide Protection against Obesity, 189

Predator Control through Learned Taste Aversion, 170

Restoring Lost Vision, 325

Scanning King Tut, 109–110

Sex, Gender, and Sports, 225

Targeting Drugs to Specific Receptors, 478

Targeting Ion Channels, 28–29

Targeting the Brain to Lessen Drug Withdrawal, 150

Total Recall, 404

Treating Pain in Limbs That Aren’t There, 368

Ultrasound Surgery, 79

Uses and Abuses of Artificial Neural Networks, 44

We Aren't the Only Tool Users, 428

What Do the Gestures of Apes and Humans Have in Common?, 305

When Binding Goes Too Far, 346

Why Bob Doesn't Jump Out of Airplanes, 250

Fusiform face area (FFA), 341, 342 (figure)

GABA. *See* Gamma-aminobutyric acid (GABA)

Gage, Phineas, 6, 60

Gall, Franz, 6

Galvani, Luigi, 5

Gambling task, 248, 248 (figure)

Gamma-aminobutyric acid (GABA), 82, 135–136, 149 (figure), 151 (table), 153, 264, 442, 488

Ganglion, 52

Ganglion cell, 316, 316 (figure), 332 (figure)

Gastric bypass procedure, 189 (figure)

Gastric juices, 171

Gate control theory, 364

Gattaca (movie), 120

Gauthier, Isabel, 341

Gelsinger, Jesse, 119

Genain quadruplets, 113 (figure)

Gender, 213

See also Biology of sex and gender

Gender dysphoria, 221

Gender identity, 213, 220–228

ablatio penis and natural experiments, 226–228

cognitive and behavioral effects, 226

46 XX intersex, 224–225

46 XY intersex, 222–224

Gender nonconformity, 230

Gender-related behavioral and cognitive differences, 217–220

Gender role, 213

General factor (g), 422

Generalized anxiety, 457 (table), 488–489

Genes, 8

addiction and, 152–155

attention-deficit/hyperactivity disorder and, 448–449

diabetes, 183

Huntingtin, 381

individuality and, 12

male same-sex behavior and, 230 (figure)

obesity, 183

schizophrenia, 461–462

See also Genetic influences/contributions

Gene therapy, 115, 119–120

Genetic Addiction Risk Score, 153

Genetic code, 8–10

Genetic engineering, 114–115

Genetic influences/contributions

addiction, 152

eating disorders, 192–193

intelligence and, 430–431

sexual orientation, 230–232

stress and, 255–258

See also Genes

Genetic predisposition, 13

Genetic similarities, 111–113

Gene expression, 11

Gene transfer, 114

Genome, 11

Genotype, 9

Genotype-Tissue Expression (GTEx) Project, 219

Geschwind, Norman, 293

Ghrelin, 175

Gilbertson, Mark, 490

Glial cells, 30–32, 39 (figure), 73, 73 (figure)

Globus pallidus, 376 (figure)

Glucagon, 173

Glucose, 171

Glutamate, 317, 362, 378

Glutamate theory, 466

Glycerol, 171

Glycogen, 172

Glymphatic activity, 515

Golgi, Camillo, 32, 95

Golgi stain, 95

Golgi tendon organs, 371

Gonads, 214, 214 (figure)

Goodall, Jane, 341

Gore, Al, 421

Graded potential, 29

Gradinaru, Viviana, 100

Grammar, 291–292

Grandin, Temple, 446

Gray, John, 217

Gray matter, 53, 66

breastmilk and, 78

criminals and, 261

drugs and, 138, 140, 153

insomnia and, 518

intelligence and, 424, 425, 429, 430 (figure), 435, 441, 448

language and, 304, 306

pain and, 366

psychological disorders and, 473, 484, 490

risk-taking and, 249

stress and, 256

See also White matter

Greebles, 341–342

Greengard, Paul, 118

Growth cones, 74

Grueter, Martina, 341

GTEx (Genotype-Tissue Expression) Project, 219

Gustation, 167–171

Gustavson, Carl, 170

Gyrus, 53, 54 (figure)

Hair cells, 278

Hallucinogenic, 141

Hamer, Dean, 230

Hammer, 277 (figure), 278

Harrison Narcotics Act, 137

Hashish, 142

Hawking, Stephen, 419, 420 (figure)

Head-related transfer function (HRTF), 288–289

Head Start program, 431

Health, and stress, 251–260

See also Emotion

Hearing, 274–291

auditory mechanism, 276–281

frequency analysis, 281–284

restoring, 284–286

sounds, 275–276, 286–291

stimulus for, 275–276

See also Language

Heath, Robert, 245

Hebb, Donald, 399

Hebb rule, 399

Hecht, Gerald, 42

Helicotrema, 278

Henderson, Jaimie, 84

Hepatic portal vein, 172

Herbivores, 167

Heredity, 8, 11–14

addiction and, 153–154

affective disorders and, 475–476

aggression and, 264–265

Alzheimer’s disease and, 409–410

anxiety, trauma, and stress-related disorders, 457, 488

autism spectrum disorder and, 443–445

intelligence and, 429–433

investigating, 111–115

obesity and, 182–185

schizophrenia, 459–462

Hering, Ewald, 321

Heritability, 12

See also Heredity

Hermann grid illusion, 329, 329 (figure)

Heroin, 131

Herr, Hugh, 375

Heterozygous, 9

Hierarchical processing, 337

High-functioning autism, 440, 445–446

Hill, Shirley, 101

Hindbrain, 64–66

Hippocampus, 136, 141, 143, 145 (figure), 146, 245 (figure), 250, 254, 255 (figure), 256, 391–396, 398–400, 402, 406–410, 414, 466–468, 472, 480, 484, 490, 514–515, 528, 536

Hitler, Adolph, 149

Hitzig, Eduard, 8

H. M. (Henry Molaison), 391–396

Hoarders, 495

Hoffman, Dustin, 445

Homeostasis, 163

simple homeostatic drives, 163–166

temperature regulation, 164–165

thirst, 165–166

See also Motivation

Homozygous, 9

Homunculus, 56

Horizontal cells, 317

Hormones

aggression and, 261–264

biological determination of sex and, 213–217

prenatal, and the brain, 216

HRTF (head-related transfer function), 288–289

Hubel, David, 332

Hubel and Wiesel's theory, 332–335

Hughes, Howard, 492, 493

Human Connectome Project, 44

Human Genome Project, 10–11, 14

Human research, 116–117

Hunger, 167–178

digestion and metabolism, 171–173

gustation and taste, 167–171

hypothalamic circuitry of, 173–174

long-term controls of, 176–178

signals for, 174–176

See also Internal states, regulation of

Hunger hormone, 175

Huntingtin gene, 381

Huntington's disease, 380–381

Hydrocephalic brain, 81 (figure), 438 (figure)

Hydrocephalus, 81, 438

Hyperpolarization, 34

Hypnotic, 131

Hypocretin, 174

Hypofrontality, 146, 467–468

Hypogonadism, 205

Hypomania, 474

Hypothalamus, 62, 164 (figure), 245 (figure)

Hypothalamus-pituitary-adrenal axis, 251

Hypovolemic thirst, 165

ID (intellectual disability), 436–438

Identity. *See* Gender identity

Identity disorders

body integrity identity disorder, 361

dissociative identity disorder (DID), 534–536

Immune cells, 253 (table)

Immune system, 252

Immunity, and stress, 251–260

Immunocytochemistry, 97, 97 (figure)

Immunohistochemical labeling, 173 (figure)

Impulsive aggression, 260

Impulsiveness, 153

INAH3. *See* Third interstitial nucleus of the anterior hypothalamus (INAH3)

Incentive theory, 163

Incidence, 458

Incubation of craving, 146

Individuality, and genes, 12

Induced pluripotent stem cells, 121

Inferior, 57 (figure)

Inferior colliculi, 62 (figure), 64, 65 (figure), 66 (table)

Inferior frontal cortex, 288 (figure)

Inferior temporal cortex, 61, 491 (figure)

Inflammatory soup, 361

Information integrator, 37

Informed consent, 117

Inhibition and excitation, 34–36

Inhibitory postsynaptic potential (IPSP), 35

Innate brain specializations, 300

Inner ear, 278–279

Inner hair cells, 279

In situ hybridization, 98, 98 (figure)

Insomnia, 518–519

Instinct, 162–163

Instrumental aggression, 260

Insular cortex, 246 (figure), 524 (figure)

Insulin, 172–173, 177, 181

Insulin receptors, 172

Integrative embodiment theory of emotions, 243

Intellectual disability (ID), 436–438

Intelligence, 419–453

abilities, 422, 423, 426–429

aging and, 433–436

animals and, 428

biological origins of, 422–433

brain and, 423–426

components of, 426

deficiencies and disorders of, 433–450

definition, 420

enhancing, 434

environmental and, 431–433

genetic controversy and, 430–431

heredity and, 429–430

meaning of, 420–422

nature of, 420–422

structure of, 422

Intelligence quotient (IQ), 420–422, 424–426, 429–434, 436–439, 441, 447

Intensity, 275

Interaural level difference, 288

Interaural timing difference, 288, 289 (figure)

Internal states, regulation of, 161–198

eating disorders, 190–194

hunger, 167–178

motivation and, 162–166

obesity, 178–190

Interneurons, 24, 24 (table)

Intracellular fluid, 25 (figure)

Intraparietal sulcus, 491 (figure)

Introspection, 505

Iodopsin, 317

Ionotropic receptors, 34

Ions, 25–28

Iproniazid, 476

IPSP (inhibitory postsynaptic potential), 35

IQ. *See* Intelligence quotient (IQ)

Iris, 316 (figure)

Itch (pruriception), 354

Jacklin, Carol, 217

James, William, 76, 243

James-Lange theory, 243

Japanese earthquake (2011), and stress-related brain damage, 256

Jenner, Bruce/Caitlyn, 201–202

Jensen, Arthur, 431

Jet lag, 507

Johnson, Virginia, 203

Kandel, Eric, 118

Kasem, Casey, 378

K complexes, 511

Keller, Helen, 306

Keller, Katherine, 427

Khachaturian, Zaven, 407

King Tut (Tutankhamun), 109

Kish, Daniel, 291

Knockout technique, 114

Knox, Johnny, 82, 82 (figure)

Koecheler, Shirley, 520

Korsakoff syndrome, 134, 414

Kuiken, Todd, 375

Labeled line coding, 168

Lange, Carl, 243

Language, 273–310

aphasia, recovery from, 297–299

Broca's area, 292–293

dialects, 303

lateralization of, 297–299

mechanism for generating, 299–302

neural and genetic antecedents, 304–306

nonhuman animals and, 302–304

reading and writing impairments, 295–297

Wernicke-Geschwind model, 292 (figure), 293–294, 295 (figure)

Wernicke's area, 293

See also Hearing

Language acquisition device, 299

Lashley, Karl, 6

Lateral, 57 (figure), 246 (figure)

Lateral fissure, 54 (figure), 56, 56 (figure), 246 (figure), 359 (figure)

Lateral geniculate nuclei, 318

Lateral hypothalamus (LH), 164 (figure), 173–174, 517, 517 (figure)

Lateral inhibition, 329, 329 (figure)

Lateralization of language, recovery from, 297–299

Lateral lemniscus, 280 (figure)

Lateral parietal cortex, 491 (figure)

Lateral ventricle, 62 (figure), 63

Learned body image, 532

Learned taste aversion, 169–170

Learned taste preferences, 170–171

Learning, 389–417

addiction and, 146–147

brain changes in, 399–405

deficiencies and disorders, 405–414

memory storage and, 390–399

sleep and, 402–403, 514 (figure)

two kinds of, 396–398

See also Memory/memories

Leary, Timothy, 141

LeDoux, Joseph, 242

Left visual field neglect, 344 (figure)

Lens, 316 (figure)

Leptin, 177, 184 (figure), 188 (figure)

Lesions/lesioning, 105

Leukocytes, 252

Levodopa (L-dopa), 378

Lewy bodies, 377–378, 521

LH. *See* Lateral hypothalamus (LH)

Light, and sleep, 508

Light, and the visual apparatus, 314–320, 332 (figure)

Light microscopy, 98–100

Limbic system, 136, 245, 245 (figure)

Lissencephalic, 51, 52 (figure)

Lithium, 483

Livingstone, David, 363

Lobotomies, 58, 59 (figure)

Localization, 6–7

Local potentials, 27, 27 (figure)

Locked-in syndrome, 526

Locus coeruleus, 516, 517 (figure)

Loewi, Otto, 33

Logothetis, Nikos, 110

Longitudinal fissure, 53, 54 (figure), 246 (figure)

Long-term depression (LTD), 399

Long-term memory, 393

Long-term potentiation (LTP), 399–402

Lorber, John, 81

Lordosis, 216

Lorenzo's Oil (movie), 115

Loudness, 275

Lou Gehrig's disease (amyotrophic lateral sclerosis), 419

Love, 212–213

Lucid dreamers, 522

Lumpers, 422

Lysergic acid diethylamide (LSD), 141

Maccoby, Eleanor, 217

Mach Band illusion, 329 (figure), 331 (figure)

Macrophages, 252

Magnetic resonance imaging (MRI), 107, 107 (figure), 241

Magnocellular nucleus, 517 (figure)

Magnocellular system, 337

Major depressive disorder (MDD), 457 (table), 474

Male-female differences, 215 (figure), 218–220

Mammillary body, 245 (figure)

Mandel, Howie, 492

Mania, 474, 479, 481, 483, 485 (figure)

Mariani, Jessica, 111

Marijuana, 142–144

appetite and, 178

changing attitudes toward, 144

Master gland. *See* Pituitary gland

Masters, William, 202

Masters of Sex (TV show), 203

Materialistic monism, 4

Mathematical performance, and the brain, 423, 426–427, 434

McGaugh, James, 404, 532

MDMA (methylenedioxymethamphetamine), 141

Medial, 57 (figure)

Medial amygdala, 207

Medial geniculate body, 280 (figure)

Medial preoptic area (MPOA), 206–207

Median preoptic nucleus (MnPO), 165, 166 (figure)

Medulla, 62 (figure), 65, 365 (figure)

Meissner's corpuscle, 355 (figure)

Melatonin, 509

Melzack, Ronald, 364

Membrane, 22 (figure)

Memory/memories, 389–417

aging and, 406

amnesia, 391–392
autobiographical, 397
changing, 403–405
consolidation of, 392–395, 402–403
declarative, 397
episodic, 397
extinction of, 403
long-term, 393
nondeclarative, 397
relational, 397
retrieval of, 392–395, 405
semantic, 397
sense of self and, 533
short-term, 393
sleep and, 514–515
spatial, 397
storage, 390–399
total recall, 404
working, 398–399
See also Learning
Men Are from Mars, Women Are from Venus (Gray), 217
Meninges, 68

Menon, Vinod, 427

Mental age, 420

Mental disorders. *See* Psychological disorders

Merkel's disks, 355 (figure)

Mescaline, 141

Mesocorticolimbic dopamine system, 145 (figure), 146

Mesolimbic pathway, 145

Messenger ribonucleic acid (mRNA), 98

Met158 allele, 152

Metabolic syndrome, 186

Metabolism

    digestion and, 171–173

    reduced, and obesity, 185–186

Metabotropic receptors, 34

Methadone, 148

Methamphetamine, 138–139

Methylation, 154, 184, 185 (figure)

Methylenedioxymethamphetamine (MDMA), 141

Michael J. Fox Foundation for Parkinson's Research, 354

Microdialysis, 104 (figure)

Microelectrodes, 102

Microglia, 252–253

Midbrain, 62 (figure), 64–66, 280 (figure), 365 (figure)

Middle cingulate cortex, 491 (figure)

Middle ear, 276, 277 (figure), 278

Middle prefrontal cortex, 491 (figure)

Migration, of the nervous system, 73

Mind-brain problem, 3

Minimally conscious, 526

Miranda, Adrian, 150

Mirror neurons, 244, 533–534

Mitchell, John, 445

Mitchell, S. Weir, 532

Mitochondria, 8

MnPO (median preoptic nucleus), 165, 166 (figure)

Mobile phones, 1–2

Model, 4

Modular processing, 337

Molaison, Henry (H. M.), 391–396

Money, John, 227

Monism, 3

Monkey brain, 55 (figure)

Monoamine hypothesis, 476

Monoamine oxidase inhibitors, 476

Monozygotic, 112

Morphine, 131

Motivation, 162

homeostasis and, 162–166

theoretical approaches to, 162–163

See also Addiction; Biology of sex and gender; Emotion; Internal states, regulation of

Motor cortex, 56, 58 (figure), 292 (figure)

prefrontal cortex, 56 (figure), 58, 247–249, 372–373

premotor cortex, 372, 373, 374 (figure)

primary motor cortex, 56, 359 (figure), 372, 376

supplementary motor cortex, 372 (figure)

Motor neurons, 22–24, 24 (table)

Mouritsen, Henrik, 97

Movement, 369–383

brain and, 372–377

disorders of, 377–383

muscles and, 369–370

perception of, 337–346

spinal cord, 370–371

See also Body senses

Movement agnosia, 343–344

MPOA (medial preoptic area), 206–207

MRI. *See* Magnetic resonance imaging (MRI)

Müller, Johannes, 77

Müllerian ducts, 214, 214 (figure)

Müllerian inhibiting hormone, 215, 224

Multiple personality disorder. *See* Dissociative identity disorder

Multiple sclerosis (MS), 382–383

Multipolar neuron, 24

Muscles

emotion and, 242–245

movement and, 369–370

Muscle spindles, 370

Myasthenia gravis (MG), 381

Myelin, 30, 31 (figure)

Myelination and conduction speed, 30–31

Myelin sheath, 23 (figure), 31 (figure)

Myelin stains, 95

Myosin, 370 (figure)

Mysophobia, 492–493

Narcolepsy, 521

Nash, John, 462

National Institutes of Health (NIH), and animal research, 118–119

Natural experiment, 112

Naturalistic observation, 93

Natural killer cells, 252

Natural selection, 12

Nature versus nurture, 8–15

genetic code, 8–10

heredity, 11–14

Human Genome Project, 10–11, 14

See also Behavioral neuroscience

Nature Neuroscience (journal), 15

Negative color aftereffect, 321

Negative symptoms, 462

Neglect, 61, 344–345

Nerve, 52

Nerve conduction velocity, 425, 426 (figure)

Nervous system, 51–88

central nervous system, 52–69

damage and recovery in, 77–83

development and change in, 71–83

development stages, 71–76

divisions of, 69 (figure)

emotion and, 242–251

modification of, through experience, 76–77

peripheral nervous system, 69–71

See also Communication, within the nervous system

Neural cells. *See* Neurons

Neural codes, 42–45

Neural inhibition, 320

Neural membrane, 24–29

Neural messages, coding of, 42–43

Neural networks, 43–45

Neural plasticity, 480

See also Plasticity

Neural tube, development of, 73 (figure)

Neurocriminology, 265–266

Neurofibrillary tangles, 407

Neurogenesis, 80

Neuroleptics, 464

Neurological anomalies, 483–486

Neuron(s), 22–30

basic structure of, 22–24

bipolar, 24

interneurons, 24, 24 (table)

mirror, 244, 533–534

motor, 22–24, 24 (table)

multipolar, 24

neural membrane, 24–29

postsynaptic neuron, 33, 34 (figure), 38 (figure), 39 (figure)

presynaptic neuron, 33, 34 (figure), 38 (figure), 39 (figure)

refractory periods, 29–30

sensory, 24, 24 (table), 66

staining and imaging of, 95–98

types of, 24, 24 (table)

unipolar, 24

See also Cell(s); Neuron communication

Neuron communication, 32–46

chemical transmission at the synapse, 33–38

neural codes and neural networks, 42–45

neurotransmitters, 39–42

synaptic activity, regulating, 38–39

See also Neuron(s); Neurotransmitters

Neuropeptide Y (NPY), 173

Neuroscience, 2

See also Behavioral neuroscience

Neurotoxins (neuron poisons), 28

Neurotransmitters, 23, 34 (figure), 39–42

aggression and, 261–264

anxiety, panic disorder, and phobia, 488–489

attention-deficit/hyperactivity disorder (ADHD) and, 448–449

representative, 40 (table)

role of, 193–194

sex and, 206–210

Neurotrophins, 75

Neutral-at-birth, 226

Newton, Isaac, 320

Nicotine, 139–140, 178

9/11 terrorist attacks, and stress-related brain damage, 256

Nissl stains, 95

Node of Ranvier, 31, 31 (figure)

Nogo-A blocker, 82

Noncoding DNA, 11

Nondeclarative memory, 397

Nondecremental, 29

Nonhuman animals, and language, 302–304

Non-REM sleep. *See* Rapid eye movement (REM) sleep

Novelty seekers, 250

Nucleus, 22, 23 (figure), 52

Nucleus accumbens, 145, 145 (figure), 209 (figure)

Nucleus laminaris, 289

Nucleus of the solitary tract (NST), 165, 168

Nurture, 8–15

See also Nature versus nurture

Obama, Barack, 44, 121

Obesity, 178–190

environment and, 182–185

gene, 183

heredity and, 182–185

myths of, 181–182

pets as possible protection against, 189

reduced metabolism, 185–186

treating, 186–189

See also Internal states, regulation of

Object agnosia, 340–342

Objects, perception of, 337–346

Observation, 92, 93

Obsession, 492

Obsessive-compulsive disorder (OCD), 457 (figure), 492–495

Obsessive-compulsive personality disorder (OCPD), 493

Obsessive-compulsive related disorders, 495–497

Occipital lobes, 56 (figure), 62, 62 (figure)

Odors, pheromones, and sexual attraction, 210–213

Ohm, Georg, 286

O’Keeffe, Georgia, 313

Olfactory system, 211

Oligodendrocytes, 30–31, 31 (figure)

Omnivores, 167

Opiates, 131–133, 364 (figure)

Opioids, 131–133

Opium, 131, 131 (figure)

Opponent process theory, 321–322

Optic chiasm, 164 (figure), 318

Optic nerve, 316 (figure), 319 (figure)

Optogenetics, 29

Optogenetic techniques, 104

Orexin, 174, 188, 517, 521

Organelles, 22

Organizing effects, 215

Organ of Corti, 277 (figure), 278

Organum vasculosum lamina terminalis (OVLT), 165

Orgasm, 203

Orientation. *See* Sexual orientation

Osmotic thirst, 165

Ossicles, 277 (figure), 278

Otoliths, 356, 357 (figure)

Outer ear, 276, 277 (figure)

Outer hair cells, 279

Out-of-body experience, 361

Oval window, 277 (figure), 278, 284

Ovaries, 214

Overdose deaths, 131–132, 133

Overweight. *See* Obesity

Ovum, 214

Oxytocin, 204, 209, 210

Pacemaker, 508

Page, Donta, 265–266

Pain, 361–368

- as an adaptive emotion, 258–260
- chronic, 365–366
- descending pain inhibition circuit, 364–365
- detecting, 355, 361–362
- dull, 361–362
- extremes of, 365–366
- insensitivity, 258, 365–366
- medications for, 362 (table)

phantom, 366–368

relief, internal mechanisms of, 363–364

sharp, 361–362

stress and, 258–260

treating, 362–363, 368

Panic disorder, 457 (table), 488–489

Parabiotic, 176

Paradoxical sleep, 512

Parafacial zone, 517

Parahippocampal gyrus, 245 (figure), 391 (figure)

Parasympathetic nervous system, 71, 72 (figure), 243 (figure)

Paraventricular nucleus (PVN), 164 (figure), 174

Parietal lobes, 59, 62 (figure)

Parieto-Frontal Integration Theory (P-FIT), 427

Parkinson’s disease, 79, 353, 377–379, 380

Parks, Kenneth, 505, 519

Parvocellular system, 337

Passive diffusion, 68 (figure)

Pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT), 516, 517 (figure)

Peek, Kim, 445

Penfield, Wilder, 61, 395

Pepperberg, Irene, 303

Peptide YY3–36 (PYY), 176

Perception, 274, 396 (figure), 399

Periaqueductal gray (PAG), 364

Peripheral nervous system (PNS), 69–71

- autonomic nervous system, 70–71, 72 (figure)
- cranial nerves, 69–70
- *See also* Nervous system

Periventricular heterotopia, 75

Personality disorders, 457 (table), 492–498

- borderline personality disorder, 457 (table), 497
- obsessive-compulsive and related disorders, 457 (table), 492–497
- Tourette syndrome, 457 (table), 495, 496

Personality factors, and stress, 255–258

Pert, Candace, 96, 132

Pets, as possible protection against obesity, 189

PET scans. *See* Positron emission tomography (PET)

PGO waves, 517

Phantom pain and limbs, 366–368, 532 (figure)

Pharmacological treatment, for drug addiction, 150–151

Phencyclidine (PCP), 141–142

Phenotype, 9

Phenylketonuria, 438

Pheromones, odors, and sexual attraction, 210–213

Phobia, 457 (figure), 488–489

Phonological hypothesis, 296

Photopigments, 316

Photoreceptors, 316, 316 (figure)

Phototherapy, 482, 519

Phrenology, 6

Physical model of behavior, 4–5

Pineal gland, 4, 63, 65 (figure)

Pinel, Philippe, 460 (figure)

Pinker, Steven, 299

Pinna, 276, 277 (figure)

Pitch, 275

Pitt, Brad, 341

Pituitary gland, 62 (figure), 63, 164 (figure)

Place cells, 395–396

Place theory, 282–284

Plagiarism, 116

Planum temporale, 297

Plaques, 407–409

Plasticity, 75, 146–147, 480, 514–515

Plateau phase, 203

Plato, 4

Pluripotent, 83

PNS. *See* Peripheral nervous system (PNS)

Polarization, 25

Polygenic, 9

Pons, 62 (figure), 65, 365 (figure)

Positive symptoms, 462

Positron emission tomography (PET), 107, 108 (figure), 259 (figure), 296 (figure), 403 (figure)

Postcentral gyrus, 56 (figure)

Posterior, 57

Posterior cingulate cortex, 491 (figure)

Posterior middle temporal gyrus, 288 (figure)

Posterior parietal cortex, 358–361, 372 (figure), 373

Postsynaptic integration, 36–38

Postsynaptic neuron, 33, 34, 38 (figure), 39, 39 (figure)

Posttraumatic stress disorder (PTSD), 255, 256, 457, 489–491

Potentiation, long-term, 399–402

Prader-Willi syndrome, 162 (figure), 175

Precentral gyrus, 56, 56 (figure)

Predator control, through learned taste aversion, 170

Predatory aggression, 260

Predisposition, 11–14

Prefrontal cortex, 56 (figure), 58, 247–249, 372–373, 395

Prefrontal-parietal network, 527

Premotor cortex, 372, 373, 374 (figure)

Prenatal hormones, and the brain, 216

Prenatal influences, and sexual orientation, 232–234

Preoptic area, 164 (figure), 165

Prescientific psychology, 3–4

Presynaptic excitation/inhibition, 38–39

Presynaptic neurons, 33, 33 (figure), 38 (figure), 39, 39 (figure), 40 (table)

Price, Jill, 404

Primary auditory cortex, 279–280, 283 (figure), 292 (figure)

Primary motor cortex, 56, 359 (figure), 372, 376

Primary somatosensory area, 359 (figure)

Primary somatosensory cortex, 59, 359–360, 359 (figure), 372 (figure)

Primary taste sensations, 168

Primary visual cortex, 292 (figure), 295 (figure), 335 (figure)

PRISM (Psychiatric Ratings Using Intermediate Stratified Markers) study, 470

Proactive aggression, 260

Progesterone, 204

Projection areas, 59

Proliferation, of the nervous system, 73

Proopiomelanocortin (POMC), 173

Proprioception, 354

ProSavin, 379

Prosody, 298–299

Prosopagnosia, 341

Protein channels, 25 (figure)

Protein kinases, 401

Psilocin, 141

Psilocybin, 141

Psychedelic drugs, 141–142

Psychoactive drugs, 130–144

- depressants, 133–136
- marijuana, 142–144
- opiates and opioids, 131–133
- psychedelic, 141–142

stimulants, 137–140
Psychological dependence, 143
Psychological disorders, 455–502, 457 (table)
affective disorders, 473–487
anxiety, trauma, and stress-related disorders, 487–492
personality disorders, 492–498
schizophrenia, 458–473
Psychology, prescientific, 3–4
Psychosis, 458
Psychosurgery, 59
PTSD. *See* Posttraumatic stress disorder (PTSD)
Pupil, 316 (figure)
Pure sounds/tones, 276
Putamen, 376 (figure)
Racism, 118
Radial arm maze, 397 (figure)
Radial glial cells, 73
Radial movement, 343–344
Raine, Adrian, 265–266
Rain Man (movie), 439, 445

Ramón y Cajal, Santiago, 33, 82, 83, 95

Raphe nuclei, 516, 517 (figure)

Rapid cycling, 483, 485 (figure)

Rapid eye movement (REM) sleep, 481, 512–518, 521, 522

- behavior disorder, 521
- functions of, 513–514
- non-REM sleep, 513–518, 520, 522

Rate law, 30

Raven Progressive Matrices, 420–421, 421 (figure), 439

Reactive aggression, 260

Reactive depression, 473–474

Reading, impairment of, 295–297

Receptive aphasia, 293

Receptive field, 317, 326 (figure), 332 (figure), 360 (figure), 374 (figure)

Receptor (sensory), 274, 277 (figure), 278, 355 (figure)

Recessive allele, 9

Recessive diabetes gene (db/db), 183

Recessive obesity gene (ob/ob), 183

Reconsolidation, of memories, 405

Reeve, Christopher, 82, 83

Reflex, 67, 68 (figure), 370–371

Refractory periods, 29–30

Regeneration, in the nervous system, 80

Reimer, David, 227

Relational memory, 397

Relationship studies, in research, 113 (table)

Relative refractory period, 30

REM sleep. *See* Rapid eye movement (REM) sleep

Reorganization, in the central nervous system, 76, 81–82

Repair, in the central nervous system, 82–83

Repolarization, 27 (figure)

Research, 91–125

- experimental versus correlational studies, 93–94
- science and theory, 92–95
- *See also* Research ethics; Research techniques

Research ethics, 115–122

- animal research, 117–119
- gene therapy, 115, 119–120
- human research, 116–117
- plagiarism and fabrication, 116

research participants, protecting the welfare of, 116–119
stem cell therapy, 120–121
See also Research
Research techniques, 95–115
brain activity, measuring and manipulating, 100–106
brain imaging techniques, 106–111
heredity, investigating, 111–115
light and electron microscopy, 98–100
neurons, staining and imaging, 95–98
See also Research
Reserve hypothesis, 413
Resolution, 203
Resting potential, 25, 27 (figure)
Restrictors, 190
Reticular formation, 65
Retina, 316, 316 (figure), 318 (figure), 319
Retinohypothalamic pathway, 510
Retinotopic map, 328
Retrieval, of memories, 392, 394 (figure)
Retrograde amnesia, 391

Retrograde stain, 95

Reuptake, 38

Reversible lesions, 105

Reward, 145, 146

See also Addiction

Reward dependent, 250

Rhodopsin, 317

Rhythms

affective disorders and, 481–483

sleep and, 507–513, 519 (figure)

Richman, Avielle, 265–266

Road rage, 262

Robo1, 74

Robo3, 74

Rohypnol (roofies or rophies), 136

Rolls, Barbara, 169, 186

Rolls, Edmund, 169

Round window, 277 (figure), 278

Ruffini ending, 355 (figure), 355

Rushton, Philippe, 431

Russell, Bertrand, 462

Rutherford, William, 281

Ryan, Anna, 520

Saccades, 296

Sacks, Oliver, 61, 340, 341, 354, 496, 532

SAD. *See* Seasonal affective disorder (SAD)

Sagittal plane, 57 (figure)

Salience network, 491, 524, 524 (figure)

Saltatory conduction, 31

Saper, Clifford, 516

Satiation, 202–204

Satiety, 166

Savage-Rumbaugh, Duane, 303

Savage-Rumbaugh, Sue, 303

Savants, 422, 445

See also Autistic savants

Scanning electron microscope, 99, 99 (figure)

Schacter, Stanley, 243

Schavan, Annette, 116

Schiller, Daniela, 489

Schizophrenia, 456, 457 (table), 458–473

- characteristics of, 458–459
- dopamine hypothesis, 463–466
- genes, search for, 461–462
- heredity and, 459–462
- neurological anomalies in, 466–473
- symptoms, two types of, 462–463
- vulnerability model, 462

Schwann cells, 31, 31 (figure)

SCID (severe combined immunodeficiency), 91, 92

Science, research, and theory, 92–95

Sclerosis, 382

SCN (suprachiasmatic nucleus), 164 (figure), 508, 508 (figure)

Seasonal affective disorder (SAD), 457 (table), 481–483

Secondary auditory cortex, 283 (figure)

Secondary motor areas, 373–375

Secondary somatosensory cortex, 360

Second-generation (atypical) antipsychotics, 465, 478

Secrets of My Life, The (Jenner), 202

Sedaris, David, 493

Sedative, 133

Selective serotonin reuptake inhibitors (SSRIs), 209, 477, 478

Selective tolerance, 138

Self. *See* Sense of self

Semantic memory, 397

Semenya, Caster, 225

Semicircular canals, 277 (figure), 357 (figure)

Sensation, 274

Sensation seeking, 163

Sense of self, 530–536

- body image and, 531–532
- disorders, 534–536
- memory and, 532–533
- mirror neurons, 533–534
- theory of mind, 533–534

Senses. *See* Body senses; Movement

Sensory gating, 469

Sensory neurons, 24, 24 (table), 66

Sensory-specific satiety, 168–169

Septal nuclei, 245 (figure)

Serotonergic psychedelics, 141

Serotonin

- aggression and, 263–264
- eating disorders and, 193–194
- levels of, and suicide, 487 (figure)
- syndrome, 465

Seth, Ankil, 527

Set point, 163

Severe combined immunodeficiency (SCID), 91, 92

Sex, 202–217

- arousal and satiation, 203–204
- as a form of motivation, 202–213
- biological determination of, 213–217
- brain structures and neurotransmitters, 206–210
- odors, pheromones, and sexual attraction, 210–213
- testosterone, 204–206
- *See also* Biology of sex and gender; Sexual orientation

Sexsomnia, 520

Sexual behavior, hormonal control of, 204–206

Sexuality-at-birth, 226

Sexually dimorphic nucleus (SDN), 207

Sexual orientation, 228–235

biological model, social implications of, 234–235

genetic and epigenetic influences, 230–232

prenatal influences, 232–234

social influence hypotheses, 229–230

See also Biology of sex and gender; Sex

SFO (subfornical organ), 165, 166 (figure)

Sharp pain, 361–362

Short-term memory, 393

Shulgin, Alexander, 142

Simmonds, Millicent, 273, 274 (figure), 285

Simner, Julia, 346

Simple cells, 333, 333 (figure)

Simulation theory, 440

Singer, Jerome, 243

Sizemore, Chris, 535

Skeletal muscles, 369

Skin conductance response (SCR), 249

Skin senses, 354–356

Sleep, 505–540

as a form of consciousness, 522

brain structures of, 515–518

circadian rhythms and, 507–511

disorders, 518–522

dreaming, 506–522

functions of, 513–514

learning and, 402–403, 514 (figure)

light and, 508

memory and, 514–515

plasticity and, 514–515

REM and non-REM, 481, 512–518, 520–522

rhythms during, 511–513

slow-wave, 511

See also Consciousness

Sleep-related eating disorder, 520

Sleep spindles, 511

Sleepwalking, 519–520

Slow-wave sleep, 511

Smith, Christine, 395

Smooth muscles, 369

Snyder, Allan, 445

Social factors, and stress, 255–258

Social impairment, and autism spectrum disorder, 439–440

Social influence hypothesis, of sexual orientation, 229–230

Sodium-potassium pump, 26

Soma (cell body), 22, 23 (figure), 24 (table), 26, 30, 35, 36 (figure), 37

Somatic nervous system, 69

Somatosensory cortex, 358–361, 367 (figure)

Somatotopic map, 358–359

Sounds

- complex, 276, 286–288
- locating, 288–291
- pure, 276

Spatial and temporal summation, 37 (figure)

Spatial frequency theory, 335–336

Spatial memory, 397

Spatial resolution, 100

Spatial rotation task, 218 (figure)

Spatial summation, 37, 37 (figure)

Speciesism, 118

Spinal cord, 22 (figure), 62 (figure), 66–67, 68 (figure), 365 (figure), 370–371

Spinal nerves, 69

Spinal reflex, 66–67, 370–371

Split brains, 534–536

Splitters, 422

Spontaneous confabulation, 414

Sports, sex/gender and, 225

Squire, Larry, 395

SSRIs (selective serotonin reuptake inhibitors), 209, 477, 478

Staining and imaging neurons, 95–98

Stem cells, 83, 84, 111

- Alzheimer’s disease and, 412
- embryonic, 83, 83 (figure)
- growing a model brain from, 111
- hearing and, 286
- movement disorders and, 378, 383
- therapy, 120–121

vision and, 325
Stereotaxic atlas, 102, 103 (figure), 105
Stereotaxic instrument, 102, 103 (figure), 105
Stereotaxic techniques, 102–105
Sternberg, Robert, 421
Steroid/peptide theory of social bonds, 210 (figure)
Stimulants, 137–140
amphetamines, 138–139
caffeine, 140
cocaine, 137–138
nicotine, 139–140
Stirrup, 277 (figure), 278
Stress, 251–260
as an adaptive response, 251–253
definition, 251
health and, 251–260
negative effects of, 253–255
pain and, 258–260
social, personality, and genetic factors, 255–258

See also Anxiety, trauma, and stress-related disorders; Emotion

Stress-diathesis model, 486

Striatum, 377

Stroke, 77

Studies, experimental versus correlational, 93–94

Subfornical organ (SFO), 165, 166 (figure)

Subgenual prefrontal cortex, 484–485

Sublaterodorsal nucleus (SLD), 518

Substance P, 362

Substantia nigra, 64, 377

Subthalamic nucleus, 376 (figure)

Sudden cardiac death, 254

Suicide, 486–487

Sulcus, 53

Superior, 57 (figure)

Superior colliculi, 62 (figure), 64, 65 (figure), 66 (table)

Supplementary motor area, 372, 374

Suprachiasmatic nucleus (SCN), 164 (figure), 508, 508 (figure)

Survey, as a research method, 93

Sylvester, Chad, 491

Sympathetic ganglion chain, 71

Sympathetic nervous system, 71

Synapse, 33–38, 38 (figure), 39 (figure)

Synaptic activity

    regulating, 38–39

    terminating, 38

Synaptic cleft, 33, 33 (figure)

Syndactyly, 76, 77 (figure)

Synesthesia, 313–314, 345, 346

Synthetic (designer) drugs, 142

Taca, Arturo, 150

Tardive dyskinesia, 464, 465

Taste, hunger and, 167–171

Taub, Edward, 118

T cell, 252

Tectorial membrane, 277 (figure), 278

Telephone theory, 281

Temperature regulation, 164–165

Temporal lobes, 56 (figure), 61

Temporal resolution, 100

Temporal summation, 37, 37 (figure)

Tensor tympani, 278

Terminals, 22–23, 23 (figure), 29, 33, 36, 38–39, 41

Testes, 214, 214 (figure), 215

Testosterone, 204–206, 262–263

Tetrodotoxin (TTX), 28

Thalamus, 62, 62 (figure), 65 (figure), 166 (figure), 245 (figure), 376 (figure), 516 (figure), 517 (figure)

THC (delta-9-tetrahydrocannabinol), 142–143

Theory, 92–95

Theory of mind, 439, 533–534

Theory theory, 439–440

Theta waves, 511

Third interstitial nucleus of the anterior hypothalamus (INAH3), 221, 233

Third ventricle, 63

Thirst, 165–166

Thomas, Craig, 375

Three Faces of Eve, The (movie), 535

Tirrell, Albert, 519

Tolerance, 130

Tolin, David, 495

Tononi, Giulio, 514, 525

Tonotopically organized, 279

Tonotopic map, 283

Topophone, 288

Total recall, 404

Tourette syndrome, 219, 457 (table), 495, 496

Tower of Hanoi problem, 396, 397 (figure)

Tracts, 52, 70

Transcranial direct current stimulation (tDCS), 106

Transcranial magnetic stimulation (TMS), 94, 105–106

Transgender, 220–221

- and the brain, 221–222
- individuals, 219–222

Transient receptor potential (TRP), 355

Transmission electron microscope, 98

Trauma. *See* Anxiety, trauma, and stress-related disorders

Traumatic brain injury (TBI), 79

Trichotillomania, 495

Trichromatic theory, of color vision, 320–321

Tricyclic antidepressants, 476

Tuberomammillary nucleus, 516

Tuning curves, 283

Twins, in studies of behavioral and medical disorders, 13 (figure), 112–113

Two-photon microscope, 99

Tympanic canal, 277 (figure), 278

Tympanic membrane, 278

Ultradian rhythms, 511

Ultrasound surgery, 79

Unipolar neuron, 24

Vaccines

antidrug, 149

childhood, and autism, 444

Vagus nerve, 175, 176

Van Horn, Jack, 60

Vegetative state, 526

Ventral, 57 (figure)

Ventral attention network, 491

Ventral horn, 66, 68 (figure)

Ventral prefrontal cortex, 484

Ventral root, 66, 68 (figure)

Ventral stream, 280, 338, 339 (figure)

Ventral tegmental area, 64, 145

Ventricles, 63

Ventrolateral prefrontal cortex, 491 (figure)

Ventrolateral preoptic nucleus, 517

Ventromedial hypothalamus (VMH), 164 (figure), 174, 207

Vesicles, 33

Vestibular canal, 277 (figure), 278

Vestibular sense, 356–357

Visible spectrum, 314–315

Vision, 313–350

- attention and, 344–345
- color, 320–328
- form, 328–337
- light, and the visual apparatus, 314–320
- perception of objects, color, and movement, 337–346
- restoring, 325
- *See also* Visual perception, disorders of

Visual acuity, 317

Visual analysis, pathways of, 337–339

Visual cortex, 56 (figure), 62, 319 (figure), 328 (figure)

Visual field, 319

Visual illusions, neural bases of, 330

Visual perception, disorders of, 340–345

color agnosia, 342–343

movement agnosia, 343–344

object and face agnosia, 340–342

visuospatial neglect and role of attention in vision, 344–345

See also Vision

Visual word form area (VWFA), 342

VMH (ventromedial hypothalamus), 164 (figure), 174, 207

Voineagu, Irene, 445

Volleying, 282, 284

Volley theory, 282

Voltage, 25

Vomeronasal organ (VNO), 211

von Békésy, Georg, 282

von Helmholtz, Hermann, 5, 282, 320

Voodoo death, 254

vos Savant, Marilyn, 419

Vulnerability, 13

Vulnerability model, and schizophrenia, 462

Wada technique, 298

Wakefield, Andrew, 116, 444

Wake therapy, 481

Waking, 511–513, 515–518

See also Sleep

Wall, Patrick, 364

Waterman, Ian, 354

Water maze, 393 (figure)

Watson, James, 8

Wavelength coded, 343

Wechsler Adult Intelligence Scale, 422

Wernicke, Carl, 292

Wernicke-Geschwind model, of language, 292 (figure), 293–294, 295 (figure)

Wernicke's aphasia, 293

Wernicke's area, 7 (figure), 56 (figure), 61, 292 (figure), 293

Wever, Ernest, 281

White matter, 45 (figure), 53–54, 66, 80, 96 (figure), 99, 107

Gage, Phineas, 60

insomnia and, 518

intelligence and, 424–425, 429, 435, 441, 448

language and, 294

marijuana and, 143

novelty seekers and, 250

psychological disorders and, 466, 469, 493

See also Gray matter

Wiesel, Torsten, 15, 332–335

Williams, Brad, 404

Williams, Justin, 534

Williams, Robin, 378

Wiltshire, Stephen, 445, 445 (figure)

Winter birth effect, 470

Wisconsin Card Sorting Test, 467

Withdrawal, 130, 150

Wolffian ducts, 214 (figure), 215

Woolf, Virginia, 242

Word salad, 293

Working memory, 398–399

Writing, impairment of, 295–298

Wundt, Wilhelm, 3, 3 (figure)

Xenomelia, 361

X-linked, 9

Young, Thomas, 320

Young-Helmholtz theory, 321

Zeitgebers, 508

Zygote, 8